Cachexia and Pre-Cachexia in Cancer Patients

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ABSTRACT

Objective: This study aimed to determine the stages of cachexia and existence of pre-cachexia in cancer patients using the parameters of the cachexia score.

Methods: The study included 333 cancer patients (males, 61.3%; mean age, 59.0 ± 13.2 years) who were followed at our clinic and received radiotherapy. The cachexia score of the patients was calculated, and their cachexia stages and pre-cachexia status were evaluated using the parameters of cachexia scoring system.

Results: According to the cachexia score of the patients, 30.9% had severe cachexia and 5.7% had terminal cachexia. The frequency of severe+terminal cachexia was the highest in gastric cancer (92.9%), followed by pancreas (57.1%) and lung (51.2%) cancers. Moreover, the frequency of severe+terminal cachexia was also the highest in the patients who received chemotherapy+radiotherapy+surgery (44.2%).

Conclusion: Assessing cachexia in the early period and planning nutritional support as a part of treatment is essential. Patients with gastrointestinal or lung cancer need to be monitored for cachexia more closely.

Keywords: Cancer cachexia, cancer, cachexia scoring system, pre-cachexia

INTRODUCTION

Cachexia is a multifactorial condition frequently encountered in cancer patients and has an impact on treatment, prognosis, quality of life, and survival. Cancer cachexia is characterized by muscle wasting (with or without loss of fat mass) and causes progressive dysfunction.[1]

Although cancer cachexia is a common condition in clinical practice, there are difficulties in its early diagnosis. One of the reasons for this includes the differences among diagnostic criteria.[2] Definitions of cachexia focus only on weight loss; conventionally, it is defined as a certain weight loss within a certain period of time such as "weight loss by ≥5% in the last 6 month." Studies on more comprehensive definitions taking body composition, physical functioning, and molecular biomarkers into account are ongoing; however, these definitions have not been included in clinical practice yet.[1,2] In addition to the need for clear and objective diagnostic criteria, one of the essential requirements for both clinical trials and patient treatment is a staging system that enables cancer patients to be classified according to the severity of cachectic syndrome. A staging system assessing the severity of cachexia will also be beneficial while deciding the type of treatment.[3]

The cachexia score (CASCO) is a scoring system used for the staging of cachectic cancer patients.[4] The scoring system takes the following 5 factors into account: body weight and lean body mass; inflammatory, immunological, and metabolic disturbances; physical performance; anorexia; and quality of life.[4] The present study aimed to determine the stages of cachexia in cancer patients using the parameters of the scoring system.

METHODS

Patients

Adult patients (> 18 years old) who received radiotherapy for cancer and were planned to receive nutrition therapy were enrolled in the study. Cachexia scoring was performed for the patients prior to radiotherapy. This study was approved by the Clinical Research Ethics Committee (24.12.2015/ E-15-714) and has been performed in accordance with the ethical standards as laid down in the

1964 Declaration of Helsinki and informed consent was obtained from all individual participants included in the study.

Cachexia Score

The cachexia scoring system includes a number of comprehensive measurements. Physical or biochemical tests are used together with related questionnaires completed by the patient him/herself.[4] In the present study, CASCO was calculated by the formula: cachexia score = BWC (0-40) + IMD (0-20) + PHP (0-15) + ANO (0-15) + QOL (0-10); where BWC indicates body weight loss and composition, IMD indicates inflammation/metabolic disturbances/immunosuppression, PHP indicates physical performance, ANO indicates anorexia, and QOL indicates quality of life. The CASCO ranges between 0 and 100 and classifies cachexia as mild cachexia (a score of 0-25), moderate cachexia (a score of 26-50), severe cachexia (a score of 51-75), and terminal cachexia (a score of 76-100).

Parameters Used for Scoring and the Questionnaires

Parameters used for the evaluation of cachexia and their scores are presented in Table 1 (BWC, IMD, PHP, ANO, anorexia, QOL, C-reactive protein (CRP), hemoglobin (Hb), Simplified Nutritional Appetite Questionnaire (SNAQ).

The questionnaire used for the evaluation of physical performance is presented in Table 2.

The SNAQ was used to evaluate anorexia (Table 3).

Main Points

- Clinicians should give importance to the nutrition of the patient as much as they give to the treatment of cancer. Our study revealed that the frequency of severe+terminal cachexia was the highest in the group that received chemotherapy+radiotherapy+surgery. The idea of only "curing cancer" is not acceptable because the patient with malnutrition may also have to interrupt or postpone cancer treatment.

- Early recognition of cachexia and management before it progresses is almost essential, as treatment would be much more challenging in advanced cases like refractory cachexia. According to the cachexia score of the patients, 30.9% were classified as severe cachexia and 5.7% were classified as terminal cachexia.

- Cachexia is not just a "weight loss." In addition to weight loss, as we used in that study, lean body mass; inflammatory, immunological, metabolic changes; physical performance; anorexia; and quality of life are also important. A scoring system that takes all these into account may help with early diagnosis and prompt initiation of treatment.

The questionnaire used for evaluating the quality of life is presented in Table 4.

Evaluation of Pre-Cachexia

Cachexia-related conditions such as inflammation and decreased physical activity might have already occurred in subjects having no significant weight loss yet (≤5% in the last 12 months) and usually having an underlying disease associated with cachexia. This is called pre-cachexia. However, despite many recommendations, there is yet no consensus on how pre-cachectic patients would be classified. If the sum of different parameters, excluding particularly the weight loss and body composition, in the patient is at least 35, this means there is pre-cachexia (4). In the present study, pre-cachexia was calculated using the formula: (BWC = 0, (IMD + PHP + QOL + ANO) > 35). As was mentioned before, the absence of significant weight loss is required for the diagnosis of pre-cachexia.

Statistical Analysis

The Predictive Analytics Software Statistics 18.0 for Windows (SPSS Inc., Chicago, Ill, USA) was used for statistical analyses. Descriptive statistics were expressed as number and percentage for categorical variables and as mean and standard deviation for numerical variables. Normality of data was analyzed using the visual (histogram and probability graphics) and analytic (Kolmogorov–Smirnov/Shapiro–Wilk tests) methods. The Mann–Whitney U-test was used for 2 group comparisons for nonnormally distributed numerical variables. Two-group and multiple-group comparisons for categorical variables were performed using the chi-square test or, if chi-square condition was not provided, by Fisher's exact test. The level of statistical significance was accepted as $P < .05$.

RESULTS

The study included 333 cancer patients with a mean age of 59.0 ± 13.2 years, of whom 61.3% were males. The general characteristics of the patients are demonstrated in Table 5.

According to the CASCO of the patients, 30.9% were classified as severe cachexia and 5.7% were classified as terminal cachexia (Table 6).

Comparison of the patients with mild+moderate cachexia and those with severe+terminal cachexia in terms of characteristics other than those included in the staging system revealed no difference regarding age, gender, smoking status, alcohol consumption, and presence of comorbidity. Vitamin D level was found to be significantly lower in the patients with severe+terminal cachexia (Table 7).

Table 1. Parameters Used for Evaluation of Cachexia and Their Scores*				
	Contribution to the Score (%)	Measurement	Score	Total Score
BWC	40	Weight loss		32
		<5%		
		≥5%, mild		
		≥10%, moderate		
		≥15%, severe		
		≥20%, terminal		
		Lean body mass		8
		Unchanged lean body mass		
		Loss of lean body mass		
IMD	20	Inflammation,		8
		Plasma CRP, mg/L		
		≤ 10		
		> 10 to ≤ 20		
		>20		
		Metabolic disorders		8
		Plasma albumin < 3.2 g/dL		
		Plasma pre-albumin < 16 mg/dL		
		Plasma lactate > 2.2 mM		
		Plasma triglycerides > 200 mg/dL		
		Anemia, Hb < 12 g/dL		
		Plasma urea > 50 mg/dL		
		Immunosuppression		4
		Peripheral lymphocytes: assessment of proliferation or positive skin hypersensitivity reaction		
PHP	15	Physical performance, questionnaire, or monitoring		15
		Total activity		
		Handgrip strength		
		Stair climbing		
		6-minute walk distance		
ANO	15	SNAQ		15
QoL	10	Quality of life questionnaire		10
		Mild		
		Moderate		
		Severe		

*It was benefited from the CASCO (4) scoring system.
ANO, anorexia; IMD, inflammation/metabolic disturbances/immunosuppression; PHP, physical performance; QoL, quality of life; SNAQ, Simplified Nutritional Appetite Questionnaire.

When the distribution of cachexia status among cancer types was evaluated, the high rate of severe+terminal cachexia (92.9%) in the patients with gastric cancer was striking (Table 8).

Evaluation of cachexia stage according to the treatment revealed that the frequency of severe+terminal cachexia was the highest in the group that received chemotherapy+radiotherapy+surgery (44.2%; Table 9).

DISCUSSION

Nutritional intervention in addition to treatment has been demonstrated to have favorable effects on prognosis and/or QoL in various types of cancer.[5,6] Early diagnosis of malnutrition or cachexia in cancer patients helps with the decision of providing nutritional support or pharmacological treatment when necessary.[7] It has been reported that assessment of baseline nutritional status of cancer patients should be a part of routine clinical practice and that nutritional intervention might be required in pre-cachexia period.[8]

In addition to the currently available scoring systems used to assess nutritional status and to determine cachexia in cancer patients, there are new scoring systems recommended by various study groups.[9-16] Nevertheless, a generally accepted objective definition or classification system is still lacking. It has been reported that evaluations performed using different criteria yield different outcomes related to nutritional status and hence the prevalence of cachexia ranges widely based on the criteria used.[17,18] This makes comparison between the studies performed using different scoring systems difficult. The present study used a CASCO including the following parameters: body weight and lean body mass; inflammatory, immunological, and metabolic disturbances; PHP; ANO; and QoL.

Weight loss in cancer patients results from the imbalance between energy intake and energy consumption. In a study performed on adult cancer outpatients presenting for diagnosis or therapy or follow-up, 1000 patients from 17 centers were evaluated in terms of nutritional status and a significant weight loss (≥10%) was observed in 39.7% of these patients.[19] It has been reported that the rate of weight loss is higher in advanced ages[20] and in certain types of cancer (lung, gastrointestinal).[21] Weight loss in the early period is associated with poor prognosis.[22] In the scoring system used in the present study, a weight loss of ≥5% and loss of lean body mass were taken into account.

Table 2. Assessment of Physical Performance*

Questionnaire
 During the past week:
   Have you noticed any particular decrease in your routine daily physical activities (i.e., at work, at home, at leisure, etc.)?
   Have you had any problems doing strenuous activities, like carrying a heavy shopping bag or suitcase?
   Have you noticed any loss of handgrip force?
   Did you have to put more effort on climbing stairs??
   Have you felt tired after walking approximately half a kilometer?

Monitoring**
   Total physical activity
   Grip force
   Stair-climb
   6-minute walk distance

*It was benefited from the CASCO (4) scoring system.   **The results of the measurements performed concurrently with the questionnaire were evaluated.

Table 3. Simplified Nutritional Appetite Questionnaire
My appetite is

a. Very poor
   b. Poor
   c. Average
   d. Good
   e. Very good

When I eat

a. I feel full just after eating only a few mouthfuls
   b. I feel full after eating about a third of a meal
   c: I feel full after eating over half a meal
   d. I feel full after eating most of the meal
   e. I hardly ever feel full.

Foods tastes

a. Very bad
   b. Bad
   c. Moderate
   d. Good
   e. Very good

Normally I eat

a. Less than one meal a day
   b. One meal a day
   c. Two meals a day
   d. Three meals a day
   e. More than three meals a day

*It was benefited from the CASCO (4) scoring system.   a=1, b=2, c=3, d=4, e=5.

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Table 4. Quality of Life Questionnaire
During the past week
Did you need to stay in bed or a chair all day long? Did you need help while eating, dressing, washing yourself, or using the toilet? Were you limited in doing either your work or other daily activities? Were you limited in pursuing your hobbies or other leisure time activities? Were you short of breath? Have you had pain? Did you need to rest? Have you had trouble sleeping? Have you felt weak? Have you felt nauseated? Have you vomited? Have you been constipated? Have you had diarrhea? Did pain interfere with your daily activities? Have you had difficulty in concentrating on things like reading a newspaper or watching television? Did you feel tense? Did you worry? Did you feel irritable? Did you feel depressed? Have you had difficulty remembering things? Has your physical condition or medical treatment interfered with your family life? Has your physical condition or medical treatment interfered with your social activities? How would you rate your overall health status during the past week? How would you rate your overall quality of life during the past week?
**It was benefited from the CASCO (4) scoring system. For the first 22 questions: not at all: 1, a little: 2, quite a bit: 3, very much: 4; last 2 questions: excellent: 1, good: 2, poor: 3, very poor: 4.

Table 5. General Characteristics of Cancer Patients	
Characteristics	
Age, year	59.01 ± 13.2
Gender	
Male	204 (61.3)
Female	129 (38.7)
Body mass index, kg/m²	26.4 ± 5.17
Diagnosis	
Breast cancer	69 (20.7)
Lung cancer	43 (12.9)
Head and neck cancer	42 (12.6)
Prostate cancer	34 (10.2)
Rectum cancer	34 (10.2)
Gastric cancer	28 (8.4)
Brain tumors	23 (6.9)
Pancreas cancer	14 (4.2)
Bladder cancer	11 (3.3)
Lymphoma	8 (2.4)
Metastasis	6 (1.8)
Multiple myeloma	4 (1.2)
Other	17 (5.1)
Data are presented as mean ± standard deviation or number (%), where appropriate.	

Chronic systemic inflammatory response has been suggested as one of the underlying mechanisms of cancer cachexia. Various clinical studies have demonstrated the relationship between cachexia and inflammatory biomarkers (acute phase proteins such as CRP and albumin and cytokines such as interleukin-6) in various types of cancer and these biomarkers are used in cachexia scoring systems.[12,21,23-28] As a convenient, sensitive, and specific test available in routine laboratory analyses, CRP is one of the parameters most frequently used in assessing inflammatory response. It is known that survival is poorer in cancer patients with high CRP levels.[21] Evaluation of high CRP level (> 10 mg/L) together with low albumin level (< 35 g/L) has been reported to have prognostic value in cancer patients.[21,25,29,30] In the scoring system used in the present study, CRP and albumin levels were also taken into account.

Performance status is one of the parameters used in the definition and classification of cachexia. The tools frequently used for this purpose by the researchers include the Eastern Cooperative Oncology Group performance status.[11,13,14] In the present study, in addition to the

Table 6. Distribution of Cancer Patients Among Cachexia Stages and Their Pre-cachexia Status	
Cachexia Stage	**n (%)**
Mild	30 (9.0)
Moderate	181 (54.4)
Severe	103 (30.9)
Terminal	19 (5.7)
Pre-cachexia	118 (35.4)

Table 7. Characteristics of the Patients According to the Cachexia Stage	Patients with Mild + Moderate Cachexia n = 211	Patients with Severe + Terminal Cachexia n = 122	P
Gender			
Male	124 (58.8)	80 (65.6)	.219
Female	87 (41.2)	42 (34.4)	
Age, year	58.66 ± 13.4	59.61 ± 12.87	.382
Vitamin D level, ng/mL	15.02 ± 12.05	13.61 ± 12.51	**.033**
Alcohol consumer	7 (3.3)	3 (2.5)	.751
Smoker	30 (14.2)	14 (11.5)	.476
Presence of comorbidity	90 (42.7)	46 (37.7)	.376

Data are presented as mean ± standard deviation or number (%), where appropriate.

Table 8. Distribution of Cachexia Status Among Cancer Types	n	Mild + Moderate Cachexia n (%)	Severe + Terminal Cachexia n (%)
Breast cancer	69	56 (81.2)	13 (18.8)
Lung cancer	43	21 (48.8)	22 (51.2)
Head and neck cancer	42	31 (73.8)	11 (26.2)
Prostate cancer	34	26 (76.5)	8 (23.5)
Rectum cancer	34	26 (76.5)	8 (23.5)
Gastric cancer	28	2 (7.1)	**26 (92.9)**
Brain tumors	23	13 (56.5)	10 (43.5)
Pancreas cancer	14	6 (42.9)	8 (57.1)
Bladder cancer	11	8 (72.7)	3 (27.3)
Lymphoma	8	4 (50.0)	4 (50.0)
Metastasis	6	3 (50.0)	3 (50.0)
Multiple myeloma	4	4 (100.0)	0 (0.0)
Other	17	11 (64.7)	6 (35.3)

The significant bold values are represented as majority of the patients.

questionnaire adapted from the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30,[4] grip strength, stair climbing, and 6-minute walk tests were used to assess the performance status.

Anorexia is a common characteristic symptom of cancer patients and is a parameter found in various scoring systems used for the evaluation of cachexia.[11,13] In the present study, SNAQ was used in assessing anorexia.

Cancer cachexia is closely associated with poorer quality of life. The EORTC QLQ-C30 is one of the scoring systems used frequently for assessing the quality of life.[13,18] Quality of life is poor also in patients with cancer cachexia.[13,14] In the present study, quality of life was assessed using the questionnaire adapted from the EORTC QLQ-C30.[4]

In the present study, of 333 cancer patients, 30.9% were determined to have severe cachexia and 5.7% were determined to have terminal cachexia using the scoring system composed of aforementioned parameters.

Cachexia is also associated with the type of cancer. It has been reported that weight loss is higher and weight loss and decreased performance appear in the early stages in patients with gastrointestinal cancer and lung cancer.[19,21,31]

Additionally, it has been reported that the prevalence of malnutrition is over 80% in elderly patients (≥ 65 years) receiving chemotherapy for cancer and malnutrition is more prevalent in those with digestive cancer than in those with nondigestive cancer.[20] In the present study, the frequency of severe+terminal cachexia was the highest in gastric cancer (92.9%), followed by pancreas (57.1%) and lung (51.2%) cancers.

Assessing cachexia, which is prevalent in cancer patients, in the early period and planning nutritional support as a part of treatment is essential because they are not fed enough. Patients with gastrointestinal or lung cancer need to be monitored for cachexia more closely. A scoring system based on more objective and comprehensive criteria and allowing also staging should be preferred.

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Table 9. Cachexia Stage According to the Treatment

	n	Mild + Moderate Cachexia n (%)	Severe + Terminal Cachexia n (%)
Chemotherapy + radiotherapy + surgery	156	87 (55.8)	**69 (44.2)**
Chemotherapy + radiotherapy	98	63 (64.3)	35 (35.7)
Radiotherapy + surgery	39	33 (84.6)	6 (15.4)
Radiotherapy	38	26 (68.4)	12 (31.6)
Chemotherapy + surgery	2	2 (100.0)	0 (0.0)
The significant bold values are represented as majority of the patients.			

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