The impact of cachexia on dietary intakes, symptoms, and quality of life in advanced cancer

Koji Amano1,2, Vickie E. Baracos3, Tatsuya Morita4, Tomofumi Miura5, Naoharu Mori2, Ryoei Tatara6, Takaomi Kessoku7, Akihiro Tokoro8, Keita Tagami9, Hiroi Shiiki1, Hiromichi Matsuoka16, Nobuhisa Nakajima12, Erika Nakanishi13,14, Jun Kako15, Daisuke Kuichi1, Hiroto Ishiki1, Hiromichi Matsuoka15, Eriko Satomi1 & Mitsunori Miyashita13

1Department of Palliative Medicine, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan; 2Department of Palliative and Supportive Medicine, Graduate School of Medicine, Aichi Medical University, 1-1 Yazakokarimata, Nagakute, Aichi 480-1195, Japan; 3Division of Palliative Care Medicine, Department of Oncology, University of Alberta, Cross Cancer Institute, Edmonton, Alberta, Canada; 4Palliative and Supportive Care Division, Seirei Mikatohara General Hospital, Hamamatsu, Shizuoka, Japan; 5Department of Palliative Medicine, National Cancer Center Hospital East, Kashiwa, Chiba, Japan; 6Department of Palliative Medicine, Osaka City General Hospital, Osaka, Osaka, Japan; 7Department of Palliative Medicine, Yokohama City University Hospital Department of Gastroenterology and Hepatology, Yokohama City University Graduate School of Medicine, Yokohama, Kanagawa, Japan; 8Department of Psychosomatic Internal Medicine and Supportive and Palliative Care Team, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Osaka, Japan; 9Department of Palliative Medicine, Tokoh University Graduate School of Medicine, Sendai, Miyagi, Japan; 10Department of Palliative Care Team, and Palliative and Supportive Care, St. Mary’s Hospital, Kurume, Fukuoka, Japan; 11Department of Clinical Oncology and Palliative Medicine, Mitsubishi Kyoto Hospital, Kyoto, Kyoto, Japan; 12Division of Community Medicine and International Medicine, University of the Ryukyus Hospital, Nakaomi-gun, Okinawa, Japan; 13Department of Palliative Nursing, Health Sciences, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan; 14Graduate School of Public Health, St. Luke’s International University, OMURA Susumu & Mieko Memorial St. Luke’s Center for Clinical Academia, Tokyo, Japan; 15College of Nursing Art and Science, University of Hyogo, Akashi, Hyogo, Japan; 16Department of Psycho-oncology, National Cancer Center Hospital, Tokyo, Japan

Abstract

Background The relationships between cachexia stages and the Functional Assessment of Anorexia/Cachexia Therapy Anorexia Cachexia Subscale (FAACT ACS) 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns have not been investigated in Asian patients with advanced cancer.

Methods This is a multicentre questionnaire survey conducted in palliative and supportive care settings across Japan. Consecutive patients were enrolled. Patient characteristics and anthropometric measurements were obtained. Dietary intakes and nutrition impact symptoms were also assessed. Patients evaluated their quality of life (QOL) using FAACT ACS. Subjects were divided into two groups, that is, pre-cachexia (non-cachexia) and cachexia and refractory cachexia (cachexia), based on cancer cachexia criteria from the international consensus. Comparisons were performed using the Mann–Whitney U test or chi-squared test. To evaluate the relationship between cachexia stages and FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns, adjusted odd ratios (ORs) and 95% confidence intervals (CIs) were calculated in the logistic models.

Results Among 495 patients, 378 (76.4%) responded. Due to missing data, 344 patients were classified into the non-cachexia group (n = 174) and cachexia group (n = 170), and 318 remained in the analysis of FAACT ACS. The cachexia group had a more impaired performance status, a lower body mass index, and a higher frequency of weight loss in 1 month (P = 0.021, <0.001, and <0.001, respectively). Advancing stages were associated with lack of appetite and reduced dietary intakes (P < 0.001 and P < 0.001, respectively). QOL scores were significantly worse in the cachexia group in FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns (P < 0.001, P = 0.001, and P < 0.001, respectively). In the models of FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns, significantly higher adjusted ORs than in the non-cachexia group were observed in the cachexia group [2.24 (95% CI 1.34–3.77), P = 0.002; 1.77 (95% CI 1.08–2.92), P = 0.024; and 2.18 (95% CI 1.29–3.70), P = 0.004, respectively].

Conclusions FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns are useful for identifying patients at risk of QOL that deteriorates with advancing stages in this population.

Keywords Cachexia; Advanced cancer; Dietary intake; Symptom; Quality of life; Palliative care

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Introduction

Cancer cachexia is a multifactorial syndrome that involves the ongoing loss of skeletal muscle mass with or without fat mass that cannot be fully reversed by usual nutritional support and leads to progressive functional impairment.\(^1,2\) It is characterized by a negative protein and energy balance driven by the combination of a reduced dietary intake and abnormal metabolism.\(^1,2\) Cancer cachexia is typically a syndrome of physical and psychological symptoms, including fatigue, drowsiness, lack of appetite, early satiety, and depression, leading to psychosocial distress in patients with advanced cancer.\(^3,4\) Many of these cachexia-related symptoms are considered to be nutrition impact symptoms because they compromise dietary intake and, in turn, drive weight loss (WL).\(^4,6\) Nutrition-impact symptoms are a range of symptoms that interfere with patients’ appetite and ability to ingest and digest food; however, a consensus on the definition of nutrition impact symptoms in cancer patients does not exist.\(^4\) Thus, due to the complex symptom burden of cancer cachexia, medical management of nutrition impact symptoms is considered a principal component of assessment and management of cancer cachexia.\(^7–9\) In addition, despite its high prevalence and negative impact on quality of life (QOL) in patients with advanced cancer, there is currently no standard care to manage cancer cachexia.\(^7–9\) Therefore, further studies to elucidate the symptom cluster and psychosocial distress experienced by cancer patients with cachexia and to develop a management strategy for cancer cachexia are urgently needed.\(^5–9\)

The QOL of patients with cancer is assessed using the Functional Assessment of Anorexia/Cachexia Therapy (FAACT), which is a patient-reported outcome measure originally designed to assess specific symptoms and concerns.\(^10,11\) The 12 items of the FAACT Anorexia Cachexia Subscale (ACS) specifically measure cachexia-related symptoms and concerns and may be scored alone to yield a domain score.\(^12\) In addition, the 5-item anorexia symptoms and 4-item anorexia concerns subscales derived from the 12 items of FAACT ACS were found to be useful for measuring anorexia symptoms and anorexia concerns in patients with lung cancer.\(^13\) These subscales may be applied to evaluations of the effects of treatment on cachexia syndrome in patients with advanced cancer.\(^13\)

To the best of our knowledge, the relationships between cachexia stages [pre-cachexia (non-cachexia) vs. cachexia and refractory cachexia (cachexia)] based on the criteria from the international consensus\(^1\) and FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns have not yet been investigated in Asian patients with advanced cancer receiving palliative and supportive care. Therefore, we herein conducted a multicentre cross-sectional study to examine the relationships between cachexia stages and dietary intake, cachexia-related symptoms, and QOL scores assessed by FAACT ACS in this population in Japan.

Methods

Sites and participants

The present study was part of a multicentre self-report questionnaire survey to develop measurements for evaluating eating-related distress experienced by patients with advanced cancer and family members. We performed a preplanned secondary analysis of the survey conducted in palliative and supportive care settings, that is, palliative care outpatient services, hospital palliative care teams, and palliative care units, at 11 hospitals across Japan. Palliative care outpatient services usually provide palliative and supportive care for patients with advanced cancer receiving cancer treatment, and palliative care units provide hospice care for dying patients with cancer in Japan. The survey consisted of two phases, the development phase and validation phase. The former was performed at 5 hospitals between July and September in 2020, and the latter at 11 hospitals between January and July in 2021. Consecutive eligible patients were enrolled in the present study if they were newly referred to palliative and supportive care in the participating institutes during the study period. All institutions were asked to take a sample of data up to the designated number of patients according to the size and situation of the institution. The inclusion criteria of the present study were (1) patients newly referred to palliative and supportive care, (2) patients aged 20 years or older, (3) patients diagnosed with locally advanced or metastatic cancer (including haematological neoplasms), (4) patients with awareness of the diagnosis of malignancy, and (5) patients with the ability to reply to a self-reported questionnaire. The exclusion criteria of the present study were (1) patients forbidden to eat by the primary physician for medical reasons, such as malignant bowel obstruction and dysphagia, and (2) serious psychological distress recognized in an interview with the palliative care physician. Patients who did not want to be enrolled were also excluded.

The present study was conducted in accordance with the ethical standards of the Helsinki Declaration and the ethical guidelines for medical and health research involving human subjects presented by the Ministry of Health, Labor, and Welfare in Japan and was approved by the local institutional review boards of all participating institutions. Japanese law does not require individual informed consent from participants in a non-invasive observational trial such as the present study. Therefore, we used an opt-out method rather than acquiring written or oral informed consent. If subjects did not want to participate, we requested them to return the ques-
tionnaire with ‘no participation’ indicated. The completion and return of the questionnaire were regarded as consent to participate in the present study.

**Measurement**

Patient demographics and clinical characteristics, that is, sex, age, primary cancer site, Eastern Cooperative Oncology Group Performance Status (ECOG PS), setting of care (palliative care outpatient service, hospital palliative care team, and palliative care unit), and treatment status (pre-chemotherapy, chemotherapy, and never treated/previous treatment), were obtained through self-report questionnaires.

Anthropometric measurements, for example, height, current body weight, and previous body weight, were reported by patients to calculate body mass index (BMI) and %WL in 6 months, as information on height, current body weight, and previous body weight reported by patients themselves is reliable. BMI was calculated by dividing current body weight (kg) by height (m)². %WL was calculated as follows: [current body weight (kg) – previous body weight (kg)]/previous body weight (kg) × 100.

Patients were asked to assess their dietary intakes with the ingesta-Verbal/Visual Analogue Scale (ingesta-VVAS), which uses 10-point analogue scales to estimate dietary intake in patients with cancer (high scores indicate better dietary intakes).

Patients rated cachexia-related symptoms or 19 nutrition impact symptoms (oral pain, pain, shortness of breath, fatigue, drowsiness, lack of appetite, early satiety, nausea, vomiting, constipation, diarrhoea, abnormal taste, abnormal smell, dry mouth, dental issues, difficulty swallowing, food bolus obstruction, anxiety, and depression) adopted from the Edmonton Symptom Assessment System (ESAS) and the Patient-Generated Subjective Global Assessments (PG-SGA) ranging between 0 (not at all) and 10 (overwhelming). Patients also estimated symptomatic fluid retention based on its presence or absence. ‘Symptomatic fluid retention’ was defined as fluid retention requiring medications or procedures (e.g., paracentesis) for management in this study.

Patients evaluated their QOL using FAACT ACS (high scores indicate better QOL).

**Statistical analysis**

Patient demographics and clinical characteristics were presented as numbers (%) for categorical variables or medians [interquartile range (IQR)] for continuous variables where appropriate. Dietary intakes measured by ingesta-VVAS, nutrition impact symptoms, and FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns were presented as medians (IQR).

Subjects were divided into two groups based on criteria from the international consensus. Cachexia was %WL in 6 months ≥5% or BMI < 20 kg/m² + %WL in 6 months ≥2%. Patients above or below these cut-off values were grouped as follows: the non-cachexia group (pre-cachexia) and cachexia group (cachexia and refractory cachexia). Comparisons between groups were performed using the Mann–Whitney U test or chi-squared test where appropriate.

To assess the effects of cachexia stages on FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns, estimated crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the logistic regression model were calculated. Scores for FAACT ACS 12-item, the 5-item anorexia symptoms, and 4-item anorexia concerns were median dichotomized for multivariate logistic regression analyses. A multivariate model adjusted for sex, age, the primary cancer site, ECOG PS, the setting of care, treatment status, and symptomatic fluid retention.

All results were considered to be significant if the P-value was <0.05. All analyses were performed using SPSS software Version 27.0.

**Results**

A total of 495 patients were asked to participate in the questionnaire survey, and 378 responded (response rate, 76.4%). Among these, no patients refused to participate. Thirty-four patients were excluded due to missing data for the classification of cachexia stages. Therefore, 344 patients were classified into the non-cachexia group (n = 174) and cachexia group (n = 170). Following the exclusion of 26 patients due to missing data on the scales, 318 remained in the analysis of FAACT ACS (Figure 1). There was no information captured via telemedicine despite the COVID pandemic. All patients participated in the present study after a face-to-face interview with the palliative care physician.

Patient demographics and clinical characteristics are summarized in Table 1. The proportion of male patients was 50.8% and median age was 63.0 (53.0–72.0) years. The proportion of patients with the primary cancer site in the upper/lower gastrointestinal tract was 13.1%, liver/biliary system/pancreas 15.7%, and lung 22.0%. The proportions of ECOG PS 0–1, 2, and 3–4 were 45.7%, 19.2%, and 27.5%, respectively. The proportions of palliative and supportive care settings were outpatient service 67.9%, hospital palliative care team 22.5%, and palliative care unit 3.3%. The proportion of patients receiving chemotherapy was 60.4% followed by never treated/previous treatment (26.0%).

In comparisons with the non-cachexia group, the cachexia group had a more impaired PS, a higher possibility of being...
Figure 1  Study diagram. FAACT ACS, Functional Assessment of Anorexia/Cachexia Therapy Anorexia Cachexia Subscale.

Table 1  Patient characteristics

|                          | Total (n = 378) | Non-cachexia (n = 174) | Cachexia (n = 170) | P     |
|--------------------------|----------------|------------------------|--------------------|-------|
| Sex                      |                |                        |                    |       |
| Male                     | 192 (50.8)     | 88 (50.6)              | 95 (55.9)          | 0.32  |
| Female                   | 181 (47.9)     | 86 (49.4)              | 75 (44.1)          |       |
| Age in years             |                |                        |                    |       |
| < 65                     | 201 (50.8)     | 105 (60.3)             | 87 (51.2)          | 0.009 |
| ≥ 65                     | 111 (28.0)     | 37 (21.3)              | 61 (35.9)          |       |
| Age                      |                |                        |                    |       |
| < 65                     | 201 (50.8)     | 105 (60.3)             | 87 (51.2)          | 0.009 |
| ≥ 65                     | 111 (28.0)     | 37 (21.3)              | 61 (35.9)          |       |
| Primary cancer site      |                |                        |                    |       |
| Upper and lower gastrointestinal tract | 52 (13.1) | 26 (15.0) | 24 (14.4) | 0.26 |
| Liver, biliary system, and pancreas | 62 (15.7) | 27 (15.6) | 32 (19.2) |       |
| Lungs                    | 87 (22.0)      | 35 (20.2)              | 45 (26.9)          |       |
| Others                   | 167 (42.2)     | 85 (49.1)              | 66 (39.5)          |       |
| ECOG performance status  |                |                        |                    |       |
| 0–1                      | 181 (45.7)     | 96 (55.8)              | 74 (43.5)          | 0.021 |
| 2                        | 76 (19.2)      | 37 (21.5)              | 35 (20.6)          |       |
| 3–4                      | 109 (27.5)     | 39 (22.7)              | 61 (35.9)          |       |
| Setting of care          |                |                        |                    |       |
| Outpatient service       | 269 (67.9)     | 138 (79.8)             | 110 (64.7)         | 0.005 |
| Hospital palliative care team | 89 (22.5) | 32 (18.5) | 51 (30.0) |       |
| Palliative care unit     | 13 (3.3)       | 3 (1.7)                | 2 (1.2)            |       |
| Treatment status         |                |                        |                    |       |
| Pre-chemotherapy         | 24 (6.1)       | 8 (4.6)                | 13 (7.9)           | 0.29  |
| Chemotherapy             | 239 (60.4)     | 121 (69.9)             | 104 (63.0)         |       |
| Never treated/previous treatment | 103 (26.0) | 44 (25.4) | 54 (31.8) |       |
| Body mass index (kg/m²)  | 20.8 (18.5–23.5) | 21.8 (19.2–24.4) | 19.5 (18.0–21.8)  | <0.001|
| Weight loss in 1 month, yes | 158 (48.8) | 37 (21.8) | 118 (74.2) | <0.001|
| Symptomatic fluid retention, yes | 80 (21.2) | 43 (25.0) | 29 (17.3) | 0.081 |

Note: Values represent n (%) or medians (interquartile ranges) where appropriate. The sums of some percentages were not 100% due to missing values. Thirty-four subjects were excluded due to missing data for the classification of cachexia stages.

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
admitted to a general ward or palliative care unit, a lower BMI, and a higher frequency of WL in 1 month (P = 0.021, 0.005, <0.001, and <0.001, respectively). However, there was no significant difference in frequency of symptomatic fluid retention (P = 0.081) (Table 1).

Relationships between cachexia stages and the means and medians of dietary intakes and nutrition impact symptoms are shown in Table 2. The mean ± standard deviation and median of dietary intakes measured by ingesta-VVAS were 6.7 ± 2.6 and 7.0 in the non-cachexia group and 5.2 ± 2.5 and 5.0 in the cachexia group. The scores of dietary intakes significantly decreased in the cachexia group (P < 0.001). Advancing stages were associated with reduced dietary intakes.

In comparisons with the non-cachexia group, the cachexia group had almost equal or worse scores in all nutrition impact symptoms. In the cachexia group, symptoms with mean or median scores ≥3 were pain, fatigue, drowsiness, lack of appetite, early satiety, and constipation. Symptoms with significant differences between the groups were lack of appetite, nausea, vomiting, abnormal taste, and abnormal smell; however, the scores of these symptoms, except for lack of appetite, were 1 or 2 in both groups. Because the scores for pain, fatigue, drowsiness, early satiety, and constipation were moderate, even in the non-cachexia group, no significant differences were observed between the groups.

The relationships between cachexia stages and the means and medians of FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns are shown in Table 3. QOL scores were significantly worse in the cachexia group than in the non-cachexia group in FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns (33.0 ± 7.6, 34.0 vs. 29.7 ± 8.3, 29.0, P < 0.001; 14.1 ± 4.4, 15.0 vs. 12.4 ± 4.7, 13.0, P = 0.001; 10.7 ± 3.0, 11.0 vs. 9.4 ± 2.9, 10.0, P < 0.001, respectively). Advancing stages were associated with deteriorating QOL scores assessed by FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns.

Adjusted ORs for cachexia stages and other variables associated with FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns are shown in Tables 4–6, respectively. In the model of FAACT ACS 12-item, a significantly higher adjusted OR than in the non-cachexia group was observed in the cachexia group [2.24 (95% CI 1.34–3.77), P = 0.002] (Table 4). Additionally, in the models of FAACT ACS 5-item anorexia symptoms and FAACT ACS 4-item anorexia concerns, significantly higher adjusted ORs than in the non-cachexia group were observed in the cachexia group [1.77 (95% CI 1.08–2.92), P = 0.024; 2.18 (95% CI 1.29–3.70), P = 0.004, respectively] (Tables 5 and 6). Only cachexia stages maintained significant differences through all models and were shown to be predictive of the likelihood of impaired QOL in this population. Because ECOG PS and symptomatic fluid retention had significant differences in two models, they were also important parameters.

**Discussion**

To the best of our knowledge, this is the first study to investigate the relationship between cachexia stages and FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns.

### Table 2: Relationships between cachexia stages and dietary intakes and nutrition impact symptoms

| Dietary intake | Total (n=378) | Non-cachexia (n=174) | Cachexia (n=170) | P | Effect size |
|----------------|--------------|----------------------|-----------------|---|-------------|
| Oral pain      | 1.0 ± 2.1, 0.0 | 0.9 ± 1.8, 0.0 | 1.1 ± 2.3, 0.0 | <0.001 | 0.58 |
| Pain #         | 3.1 ± 3.1, 2.0 | 3.2 ± 3.2, 2.0 | 3.1 ± 3.0, 2.0 | 0.093 | 0.03 |
| Shortness of breath | 1.8 ± 2.5, 1.0 | 1.6 ± 2.4, 0.0 | 2.0 ± 2.5, 1.0 | 0.16 |
| Fatigue        | 3.2 ± 2.8, 3.0 | 3.3 ± 2.9, 3.0 | 3.1 ± 2.6, 3.0 | 0.07 |
| Drowsiness     | 3.1 ± 2.9, 3.0 | 3.2 ± 2.9, 3.0 | 3.1 ± 2.7, 3.0 | 0.00 |
| Lack of appetite #, * | 3.3 ± 2.9, 3.0 | 2.6 ± 2.7, 2.0 | 3.9 ± 3.0, 3.0 | <0.001 |
| Early satiety #, * | 3.7 ± 3.0, 3.0 | 3.5 ± 3.1, 3.0 | 3.8 ± 2.9, 3.5 | 0.10 |
| Nausea #       | 1.6 ± 2.4, 0.0 | 1.2 ± 2.1, 0.0 | 2.0 ± 2.6, 1.0 | 0.004 |
| Vomiting #     | 0.9 ± 2.1, 0.0 | 0.7 ± 1.8, 0.0 | 1.2 ± 2.4, 0.0 | 0.24 |
| Constipation   | 3.2 ± 3.1, 3.0 | 2.9 ± 3.1, 2.0 | 3.4 ± 3.0, 3.0 | 0.16 |
| Diarrhoea      | 1.6 ± 2.5, 0.0 | 1.6 ± 2.5, 0.0 | 1.7 ± 2.5, 0.0 | 0.04 |
| Abnormal taste #, * | 1.5 ± 2.5, 0.0 | 1.0 ± 2.1, 0.0 | 2.0 ± 2.9, 0.0 | <0.001 |
| Abnormal smell #, * | 0.9 ± 2.1, 0.0 | 0.7 ± 1.8, 0.0 | 1.1 ± 2.3, 0.0 | 0.005 |
| Dry mouth      | 1.9 ± 2.7, 0.0 | 1.8 ± 2.8, 0.0 | 2.1 ± 2.7, 1.0 | 0.11 |
| Dental problems| 1.3 ± 2.5, 0.0 | 1.2 ± 2.4, 0.0 | 1.1 ± 2.3, 0.0 | 0.04 |
| Difficulty swallowing  | 1.0 ± 2.1, 0.0 | 0.8 ± 1.9, 0.0 | 1.2 ± 2.2, 0.0 | 0.19 |
| Food bolus obstruction | 1.1 ± 2.3, 0.0 | 1.0 ± 2.2, 0.0 | 1.2 ± 2.3, 0.0 | 0.09 |
| Anxiety #, **  | 2.6 ± 2.8, 2.0 | 2.5 ± 2.8, 2.0 | 2.6 ± 2.7, 2.0 | 0.04 |
| Depression #, ** | 2.7 ± 2.8, 2.0 | 2.7 ± 2.8, 2.0 | 2.8 ± 2.7, 2.0 | 0.04 |

*Note: Values represent mean ± standard deviation and median. The larger the effect size, the stronger the relationship between two variables: small (0.2), medium (0.5), and large (0.8). Symptoms with # are part of the FAACT ACS 12-item. Symptoms with * and those with ** are part of the 5-item anorexia symptoms and 4-item anorexia concerns, respectively.*

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concerns in Japanese patients with advanced cancer in palliative and supportive care settings. The results obtained demonstrated that cachexia stages were significantly and independently predictive of deteriorating QOL in this population. The findings of the present study revealed that the advanced cancer cachexia stage was strongly associated with lack of appetite and reduced dietary intakes. The result showing that the cachexia group had almost equal or worse scores than the non-cachexia group in all nutrition impact symptoms was consistent with previous findings. However, no significant differences were observed in the scores for pain, fatigue, drowsiness, early satiety, and constipation between the groups. There may be a possibility that these symptoms were evoked in the non-cachexia group due to side effects of chemotherapy to treat cancer, because around 70% received chemotherapy.

Consistent with previous findings, the severity of depression and anxiety was also moderate in patients with or without cachexia; however, no significant differences were observed between groups.

Table 3  Relationships between cachexia stages and FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns

| FAACT ACS 12-item (n = 318) | Total | Non-cachexia | Cachexia | P    | Effect size |
|-----------------------------|-------|--------------|----------|------|-------------|
| 31.4 ± 8.2, 32.0            | 33.0 ± 7.6, 34.0 | 29.7 ± 8.3, 29.0 | <0.001  | 0.40 |
| FAACT ACS 5-item anorexia symptoms (n = 316) | 13.2 ± 4.6, 14.6 | 14.1 ± 4.4, 15.0 | 12.4 ± 4.7, 13.0 | 0.001  | 0.37 |
| FAACT ACS 4-item anorexia concerns (n = 317) | 10.1 ± 3.1, 10.0 | 10.7 ± 3.0, 11.0 | 9.4 ± 2.9, 10.0 | <0.001  | 0.42 |

Note: Values represent mean ± standard deviation and median. The larger the effect size, the stronger the relationship between two variables: small (0.2), medium (0.5), and large (0.8).

Abbreviation: FAACT ACS, Functional Assessment of Anorexia/Cachexia Therapy Anorexia Cachexia Subscale.

Table 4  Estimated crude and adjusted odds ratios for a logistic regression model assessing effects of cachexia stages on FAACT ACS 12-item (below the median <32) (n = 318)

| Sex               | Crude OR (95% CI) | P    | Adjusted OR (95% CI) | P    |
|-------------------|-------------------|------|----------------------|------|
| Male              | 1.00 (reference)  |      | 1.00 (reference)     |      |
| Female            | 1.12 (0.74–1.69)  | 0.60 | 1.25 (0.75–2.08)     | 0.39 |
| Age <65           | 1.00 (reference)  |      | 1.00 (reference)     |      |
| Age 65–74         | 1.13 (0.70–1.82)  | 0.61 | 0.75 (0.40–1.39)     | 0.36 |
| Age ≥75           | 0.80 (0.44–1.43)  | 0.45 | 0.84 (0.41–1.73)     | 0.63 |
| Primary cancer site | 1.00 (reference) |      | 1.00 (reference)     |      |
| Upper and lower gastrointestinal tract | 0.79 (0.37–1.67) | 0.53 | 1.14 (0.47–2.76) | 0.78 |
| Liver, biliary system, and pancreas | 0.90 (0.45–1.83) | 0.78 | 0.78 (0.34–1.82) | 0.57 |
| Lungs             | 0.62 (0.33–1.17)  | 0.14 | 0.67 (0.31–1.41)     | 0.29 |
| Others            | 1.00 (reference)  |      | 1.00 (reference)     |      |
| ECOG performance status | 3.56 (2.03–6.26) | <0.001 | 4.01 (2.05–7.85) | <0.001 |
| Setting of care   |                  |      |                      |      |
| Outpatient service | 1.00 (reference) |      | 1.00 (reference)     |      |
| Hospital palliative care team | 1.32 (0.80–2.15) | 0.28 | 0.95 (0.52–1.73) | 0.86 |
| Palliative care unit | 11.39 (1.44–90.29) | 0.021 | 4.44 (0.47–42.27) | 0.19 |
| Treatment status  |                  |      |                      |      |
| Pre-chemotherapy  | 1.00 (reference)  |      | 1.00 (reference)     |      |
| Chemotherapy      | 0.71 (0.30–1.67)  | 0.43 | 0.76 (0.26–2.25)     | 0.62 |
| Never treated/previous treatment | 0.85 (0.34–2.13) | 0.73 | 1.12 (0.35–3.55) | 0.85 |
| Symptomatic fluid retention | 5.34 (3.14–9.11) | <0.001 | 4.59 (2.43–8.68) | <0.001 |

Note: Sixty subjects were excluded due to missing data: cachexia stages (n = 34) and FAACT ACS 12-item (n = 26). A multivariate model adjusted for sex, age, the primary cancer site, ECOG performance status, setting of care, treatment status, and symptomatic fluid retention.

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FAACT ACS, Functional Assessment of Anorexia/Cachexia Therapy Anorexia Cachexia Subscale; OR, odds ratio.
tween the groups. These results implied that psychological symptoms may occur before physical symptoms become apparent.

Pain, fatigue, drowsiness, lack of appetite, and early satiety are regarded as typical cachexia-related symptoms and overlap with sickness behaviour, which is associated with systemic inflammation and the central nervous system in infected individuals spanning from arthropods to vertebrates. Furthermore, depression and anxiety are also regarded as sickness behaviour. However, further studies are needed to investigate whether the symptom cluster in advanced cancer reflects sickness behaviour. In summary, due to the complex symptom burden of advanced cancer, the medical management of cachexia-related symptoms is considered to be a principal component of cancer cachexia management.

Not only cancer cachexia stages but also ECOG PS and symptomatic fluid retention showed significant differences in the model of 5-item anorexia symptoms (Table 5). In contrast to symptomatic fluid retention, ECOG PS did not maintain a significant difference in the model of FAACT 4-item anorexia concerns (Table 6). The results of the present study suggest that ECOG PS is an independent predictor of cachexia-related symptoms and that fluid retention is an independent predictor of cachexia-related distress in patients with advanced cancer. Furthermore, cachexia-related distress may precede the deterioration of physical function or cachexia-related symptoms.

We included symptomatic fluid retention as one of the potentially confounding factors in multivariate logistic regression analyses because we previously reported that the prevalence of fluid retention was high in patients with advanced cancer in palliative care units and also that BMI and %WL appeared to lose their true values in these patients. The relationship between fluid retention and simple anthropometric measures represents a key issue in staging cancer cachexia.
To develop a sophisticated management strategy for cancer cachexia, multiple clinical trials and appropriate QOL measurements are needed. Difficulties are currently associated with investigating the efficacy of a new drug that stimulates appetite, such as anamorelin, on QOL. However, the present results revealed the suitability of FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns in addition to the questionnaire for eating-related distress among Japanese patients with advanced cancer. Basically, FAACT ACS 12-item should be utilized, but 5-item anorexia symptoms and 4-item anorexia concerns can be secondarily used depending on the situation. These QOL measurements will contribute to further clinical trials and the development of a new care strategy for cancer cachexia in the future.

The present study has several limitations that need to be addressed. Because the present study was a cross-sectional analysis of a questionnaire survey, survival data were not obtained and the prognostic ability of each stage was not evaluated. Additionally, potential confounders may not have been obtained. It was impossible to assess other factors affecting the relationship between cachexia stages and QOL. Moreover, because fluid retention, for example, oedema, pleural effusion, and ascites, may interfere with the accurate assessment of oedema-free BMI and oedema-free %WL, it was not possible to confirm the true value of cachexia stages with non-oedematous variables in the present study. Nevertheless, the results obtained reflect the real world of patients with advanced cancer receiving palliative and supportive care. A large multicounty collaborative prospective cohort study assessing overall survival, body composition measurements, cachexia-related symptoms, cachexia-related distress, and health-related QOL in patients with incurable cancer is needed in the near future. Furthermore, approximately 70% of patients were receiving cancer-directed therapy; however, there is no information on the types (cytotoxic chemotherapy, targeted therapy, immunotherapy, and combination) or relative dose intensity.

Table 6 Estimated crude and adjusted odds ratios for a logistic regression model assessing effects of cachexia stages on FAACT ACS 4-item anorexia concerns (below the median <10) (n = 317)

|                          | Crude OR (95% CI) | P      | Adjusted OR (95% CI) | P      |
|--------------------------|-------------------|--------|----------------------|--------|
| Sex                      |                   |        |                      |        |
| Male                     | 1.00 (reference)  |        | 1.00 (reference)     |        |
| Female                   | 1.06 (0.69–1.63)  | 0.78   | 1.19 (0.72–1.99)     | 0.50   |
| Age                      |                   |        |                      |        |
| <65                      | 1.00 (reference)  |        | 1.00 (reference)     |        |
| 65–74                    | 1.37 (0.85–2.22)  | 0.20   | 1.14 (0.62–2.09)     | 0.67   |
| ≥75                      | 0.90 (0.49–1.67)  | 0.75   | 0.97 (0.46–2.05)     | 0.93   |
| Primary cancer site      |                   |        |                      |        |
| Upper and lower gastrointestinal tract | 1.00 (reference) |        | 1.00 (reference)     |        |
| Liver, biliary system, and pancreas | 1.08 (0.50–2.33) | 0.85   | 1.32 (0.55–3.21)     | 0.54   |
| Lungs                    | 1.52 (0.74–3.12)  | 0.25   | 1.52 (0.66–3.50)     | 0.33   |
| Others                   | 0.91 (0.48–1.76)  | 0.79   | 1.14 (0.53–2.44)     | 0.73   |
| ECOG performance status  |                   |        |                      |        |
| 0–1                      | 1.00 (reference)  | <0.001 | 1.86 (1.00–3.45)     | 0.050  |
| 2                        | 2.57 (1.47–4.52)  | 0.001  | 1.87 (0.96–3.64)     | 0.066  |
| 3–4                      | 3.08 (1.84–5.14)  | <0.001 | 1.99 (0.42–9.46)     | 0.39   |
| Setting of care          |                   |        |                      |        |
| Outpatient service       | 1.00 (reference)  |        | 1.00 (reference)     |        |
| Hospital palliative care team | 1.26 (0.76–2.08) | 0.37   | 1.01 (0.56–1.83)     | 0.97   |
| Palliative care unit     | 4.71 (1.22–18.18) | 0.025  | 1.99 (0.42–9.46)     | 0.39   |
| Treatment status         |                   |        |                      |        |
| Pre-chemotherapy         | 1.00 (reference)  |        | 1.00 (reference)     |        |
| Chemotherapy             | 0.95 (0.40–2.29)  | 0.91   | 1.24 (0.42–3.66)     | 0.70   |
| Never treated/previous treatment | 1.02 (0.40–2.59) | 0.97   | 1.34 (0.42–4.25)     | 0.62   |
| Symptomatic fluid retention |               |        |                      |        |
| No                       | 1.00 (reference)  |        | 1.00 (reference)     |        |
| Yes                      | 4.95 (2.84–8.62)  | <0.001 | 5.83 (3.04–11.17)    | <0.001 |
| Cachexia stage           |                   |        |                      |        |
| Non-cachexia             | 1.00 (reference)  |        | 1.00 (reference)     |        |
| Cachexia                 | 1.89 (1.21–2.96)  | 0.005  | 2.18 (1.29–3.70)     | 0.004  |

Note: Sixty-one subjects were excluded due to missing data: cachexia stages (n = 34) and FAACT ACS 4-item anorexia concerns (n = 27). A multivariate model adjusted for sex, age, the primary cancer site, ECOG performance status, setting of care, treatment status, and symptomatic fluid retention.

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FAACT ACS, Functional Assessment of Anorexia/Cachexia Therapy Anorexia Cachexia Subscale; OR, odds ratio.
Conclusions

FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns are useful for identifying patients at risk of QOL that deteriorates with advancing stages among Japanese patients with advanced cancer receiving palliative and supportive care.

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Conflicts of interest

The authors have read and understood the journal’s policy on the declaration of interest and declare that there are no conflicts of interest.

Ethics statement

The present study was conducted in accordance with the ethical standards of the Helsinki Declaration and the ethical guidelines for medical and health research involving human subjects presented by the Ministry of Health, Labor, and Welfare in Japan and was approved by the local institutional review boards of all participating institutions.