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Development and validation of questionnaires for eating-related distress among advanced cancer patients and families

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Abstract

Background Eating-related distress (ERD) is one type of psychosocial distress among advanced cancer patients and family caregivers. Its alleviation is a key issue in palliative care; however, there is no validated tool for measuring ERD.

Methods The purpose of this study was to validate tools for evaluating ERD among patients and family caregivers. The study consisted of a development and validation/retest phase. In the development phase, we made preliminary questionnaires for patients and family caregivers. After face validity and content validity, we performed an exploratory factor analysis and discussed the final adoption of items. In the validation/retest phase, we examined factor validity with an exploratory factor analysis. We calculated Pearson's correlation coefficients between the questionnaire for patients, the Functional Assessment of Anorexia/Cachexia Therapy Anorexia Cachexia Subscale (FAACT ACS) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Cachexia 24 (EORTC QLQ-CAX24) and Pearson's correlation coefficients between the questionnaire for family caregivers and the Caregiver Quality of Life Index-Cancer (CQOLC) for concurrent validity. We calculated Cronbach's alpha coefficients (Cronbach's alpha) and intraclass correlation coefficients (ICCs) for internal consistency and test–retest reliability. We performed the Mann–Whitney *U* test between the questionnaires and cancer cachexia based on criteria from the international consensus for known-group validity.

Results In the development phase, 162 pairs of patients and family caregivers were asked to participate, and 144 patients and 106 family caregivers responded. In the validation/retest phase, 333 pairs of patients and family caregivers were asked to participate, and 234 patients and 152 family caregivers responded. Overall, 183 patients and 112 family caregivers did the retest. Seven conceptual groups were extracted for the ERD among patients and family caregivers, respectively. Patient factors 1–7 correlated with FAACT ACS (r = −0.63, −0.43, −0.55, −0.40, −0.38, −0.54,

−0.38, respectively) and EORTC QLQ-CAX24 (r = 0.58, 0.40, 0.60, 0.49, 0.38, 0.59, 0.42, respectively). Family factors 1–7 correlated with CQOLC (r = −0.34, −0.30, −0.37, −0.37, −0.46, −0.42, −0.40, respectively). The values of Cronbach's alpha and ICC of each factor and all factors of patients ranged from 0.84 to 0.96 and 0.67 to 0.83, respectively. Those of each factor and all factors of family caregivers ranged from 0.84 to 0.96 and 0.63 to 0.84, respectively. The cachexia group of patients had significantly higher scores than the non-cachexia group for each factor and all factors.

Conclusions Newly developed tools for measuring ERD experienced by advanced cancer patients and family caregivers have been validated.

Keywords Cachexia; Advanced cancer; Distress; Symptom; Quality of life; Palliative care

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Introduction

Cancer cachexia is defined as a wasting disorder with a multifactorial aetiology involving the ongoing loss of skeletal muscle and adipose tissue mass and progressive functional impairments that cannot be fully reversed by usual nutritional support.[1,2] It is characterized by negative protein and energy balances driven by the combination of a reduced dietary intake and disarranged metabolism.[1,2] Cancer cachexia is a syndrome with physical and psychological symptoms in patients with cancer, including a lack of appetite, early satiety, reduced dietary intake, fatigue, drowsiness and depression. These symptoms are worsened by cancer treatments and can lead to psychosocial distress in patients.[3–5] These burdens also greatly impact on their family caregivers and relationships between patients and family caregivers.[3–5] Eating-related distress (ERD) is one type of psychosocial distress in patients and family caregivers, and its alleviation is a key issue in palliative care.[3–5] However, few studies have investigated the prevalence and severity of ERD among patients and family caregivers.[3–5] In our previous study, three factors were extracted in ERD experienced by patients as follows: (i) lack of appetite and reduced dietary intake, (ii) insufficient information about the patient's diet and eating problems and (iii) conflicts over food between patients and their family caregivers.[6] The study also reported that the cachexia group had significantly higher ERD than the non-cachexia group for each factor.[6]

To date, there are only two questionnaires that examine the cancer cachexia-related quality of life (QOL) of patients. The Functional Assessment of Anorexia/Cachexia Therapy (FAACT), which is a patient-reported outcome measure to assess specific symptoms and concerns, assesses the QOL of patients with cancer cachexia.[7,8] The 12 items of the FAACT Anorexia Cachexia Subscale (ACS) specifically measure cachexia-related symptoms and concerns, which can be scored alone to yield a domain score to assess the QOL of patients with cancer cachexia.[9–11] In addition, the five-item anorexia symptoms and four-item anorexia concerns subscales derived from the 12 items of FAACT ACS were also found to be useful for measuring anorexia symptoms and anorexia concerns.[10,11] The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Cachexia 24 (EORTC QLQ-CAX24) used in combination with EORTC Core Quality of Life Questionnaire (QLQ-C30) is also a cancer cachexia-specific questionnaire for health-related QOL assessment in clinical trials and clinical practice. It contains 24 items, comprising five multi-item scales (food aversion, eating and weight-loss worry, eating difficulties, loss of control and physical decline) and four single items.[12,13] However, both FAACT ACS and EORTC QLQ-CAX24 do not cover thoroughly ERD among patients, particularly matters of insufficient information and conflicts over food within families. Furthermore, there is currently no fully validated specific tool for measuring ERD experienced by patients.[6] Therefore, difficulties are associated with investigating the effects of new drugs stimulating the appetite in cancer cachexia on the cachexia-related distress of patients.[6] In addition, a questionnaire that measures the cancer cachexia-related QOL and distress of family caregivers has not yet been developed.[6]

There is currently no standard care to manage cancer cachexia despite its high prevalence and negative impact on the QOL of patients and family caregivers.[14–17] Therefore, the latest evidence-based clinical practice guidelines on the management of cancer cachexia, clinical nutrition in cancer and end-of-life care for patients with cancer suggest the necessity of holistic multimodal interventions to meet the physiological and psychological needs of patients and family caregivers.[14–17] However, limited information is available on the effectiveness of holistic multimodal interventions for cancer cachexia due to the lack of clinical trials, even though an ideal multimodal care team has already been conceptualized.[14–17] Therefore, to perform clinical trials with the aim of developing holistic multimodal interventions for cancer cachexia, new patient-centred and family-centred tools measuring cancer cachexia-related QOL, in particular

ERD, a subset of factors influencing QOL in cancer cachexia, are urgently needed. Newly developed tools able to measure ERD are needed to complement the existing QOL measurements, including FAACT ACS and EORTC QLQ-CAX24. Therefore, we herein conducted a full-scale validation study investigating how the new ERD questionnaires for patients and family caregivers performed compared with items or distress subscales within the already validated QOL measurements of patients and family caregivers.

Methods

Sites and participants

This study was a multicentre self-report questionnaire that was conducted in palliative care settings (i.e. palliative care outpatient services, hospital palliative care teams and palliative care units) at 11 hospitals across Japan to develop tools for evaluating ERD experienced by patients with advanced cancer and family caregivers. In Japan, palliative care outpatient services and hospital palliative care teams generally provide palliative and supportive care for patients receiving cancer treatments and their family caregivers, and palliative care units provide hospice care for dying patients with cancer and their family caregivers.

This study consisted of a development phase and validation/retest phase. The former was performed at five hospitals between July and September in 2020, and the latter at 11 hospitals between January and July in 2021. Consecutive patients and their family caregivers were screened for participation if they were newly referred to palliative care in the participating institutes during the study period, and eligible patients and their family caregivers were enrolled for the study. All participating institutions were requested to take a sample of data up to a designated number of patients of 10, 50, 70 and 100 according to the size and situation of the institution.

The inclusion criteria of patients were (i) patients newly referred to palliative care, (ii) adult patients (≥20 years), (iii) patients diagnosed with locally advanced or metastatic cancer (including haematological neoplasms), (iv) patients with awareness of the diagnosis of malignancy and (v) patients with the ability to reply to a self-reported questionnaire. Exclusion criteria were (i) patients forbidden to eat by the primary physician for medical reasons and (ii) patients with serious psychological distress (e.g. uncontrolled psychiatric disorder) recognized in an interview with the palliative care physician. Patients who did not want to be enrolled were also excluded.

The inclusion criteria of family caregivers were (i) family members of eligible patients, (ii) adult family members (≥20 years), (iii) family members with awareness of the diagnosis of malignancy and (iv) family members with the ability to reply to a self-reported questionnaire. The exclusion criterion was family caregivers with serious psychological distress (e.g. uncontrolled psychiatric disorder) recognized in an interview with the palliative care physician. When hospital visits were not allowed due to the COVID-19 pandemic, palliative care physicians asked patients about mental status of their family caregivers. Family caregivers who did not want to be enrolled were also excluded.

This study was performed 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, Labour and Welfare in Japan. The study was approved by the local Institutional Review Boards in all participating institutions. Because individual informed consent from participants is not required by Japanese law in a non-invasive observational trial, acquiring written or oral informed consent was not employed. If subjects did not want to participate, we requested return of the questionnaire with 'no participation' indicated. The completion and return of the questionnaire were regarded as consent to participate in the study.

Measurements

Information on patient demographics and clinical characteristics [e.g. age, sex, primary cancer site and the Eastern Cooperative Oncology Group performance status (ECOG PS)[18]] and data on family caregiver demographics (i.e. age, sex and relationship to the patient) were obtained through self-report questionnaires. To calculate body mass index (BMI) and weight loss (WL) in 6 months, anthropometric measurements (i.e. height, current body weight and previous body weight) were reported by patients.[19,20] BMI was calculated by dividing current body weight (kg) by height $(m)^2$, and %WL in 6 months was obtained as follows: (current body weight [kg] − previous body weight [kg])/previous body weight (kg) × 100. Cachexia was %WL in 6 months ≥5% or BMI < 20 kg/m^2 + %WL in 6 months ≥2% based on criteria from the international consensus.[1] Patients were requested to measure their dietary intakes using the Ingesta-Verbal/Visual Analogue Scale (Ingesta-VVAS), which has 10-point analogue scales to estimate dietary intake in patients with cancer (high scores indicate better dietary intakes).[21]

In the development phase, patients were asked to measure their ERD using the preliminary ERD questionnaire for patients with 42 items based on the findings of previous studies.[22–24] In the validation/retest phase, patients were asked to measure their ERD using the ERD questionnaire for patients with 21 items obtained through the development phase. Patients were also asked to complete the Japanese versions of FAACT ACS, EORTC QLQ-C30 and EORTC QLQ-CAX24.[7,8,12,13]

In the development phase, family caregivers were asked to evaluate their ERD using the preliminary ERD questionnaire for family caregivers with 42 items based on the findings of previous studies.[25,26] In the validation/retest phase, family caregivers were asked to measure their ERD using the ERD questionnaire for family caregivers with 21 items obtained through the development-phase. Family caregivers were also asked to complete the Japanese version of the Caregiver Quality of Life Index-Cancer (CQOLC).[27,28]

Patients and family caregivers who had completed and returned the first tests were asked to do retests within a week after answering the first tests in the validation/retest phase because of the potential for rapid change in condition in a subject receiving palliative care. However, subjects were instructed not to do retests on the same day of the first tests.

Sample size

We planned to perform an exploratory factor analysis in the both development phase and validation/retest phase to explore the factor structure, but there is no established method for calculating the required number of cases in such studies. Generally, 5–10 times as many subjects as the number of items are needed to conduct factor analysis. In addition, the COSMIN study design checklist for patient-reported outcome measurement instruments suggests that a sample of $\geq$100 patients is very good.[29] We calculated the sample size based on the assumption that a 20-item rating scale was to be created considering expected number of missing values. Based on the results of the previous studies,[23,24] a response rate for patients was expected 80%, and that for family caregivers was estimated 80% of the patient response rate.

Statistical analysis

Patient and family caregiver demographics and clinical characteristics are presented as numbers (%) for categorical variables or as means ± standard deviations (SD) for continuous variables where appropriate. All results were considered to be significant if the *P*-value was less than 0.05. All analyses were performed using the statistical package SAS version 9.1 (SAS Institute, Cary, NC).

Development phase

We initially developed the preliminary ERD questionnaires for patients with 42 items and for family caregivers with 42 items based on our previous studies.[22–26] In order to check the face validity and content validity, the items were given to five patients to review the items in terms of writing, meaning and ambiguity and give us feedback. After reviewing the suggestions and making the recommended changes, the revised items were given to five experts (two palliative care physicians, two nurses and one psychologist) to evaluate them in terms of content.

To extract potential latent variables, we performed an exploratory factor analysis using the principle method with a promax rotation, which is an oblique rotation allowing factors to be correlated and can be calculated more quickly than a direct oblimin rotation. Seven core domains were identified in each questionnaire, and three to five items with comprehensive meaning were selected for each domain. We also discussed the final adoption of items for the ERD questionnaires for patients and family caregivers from the point of view of clinical importance and psychological burden of respondents.

Validation/retest phase

To organize the items obtained through the development phase in the ERD questionnaires for patients and family caregivers, any items with 20% or more missing data across the sample were reviewed and excluded. Also, any item with a ceiling or floor effect, defined as 80% or more of the responses were at either end of the scale, 'absolutely disagree' or 'absolutely agree', was reviewed and excluded.

To examine the validity and reliability of the final ERD questionnaires for patients with 21 items in seven core domains and for family caregivers with 21 items in seven core domains, we examined factor validity with an exploratory factor analysis using the principle method with a promax rotation to extract potential latent variables. To examine concurrent validity, we calculated Pearson's correlation coefficients between the ERD questionnaire for patients and FAACT ACS, EORTC QLQ-C30 and EORTC QLQ-CAX24, because ERD is a subset of factors influencing QOL in cancer cachexia. We also calculated Pearson's correlation coefficients between the ERD questionnaire for family caregivers and CQOLC. Regarding internal consistency and test–retest reliability, we calculated Cronbach's alpha coefficients (Cronbach's alpha) and intraclass correlation coefficients (ICCs) in each domain of the questionnaires for patients and family caregivers.

Concerning known-group validity, we performed the Mann–Whitney *U* test between each domain of the questionnaires for patients and family caregivers and cancer cachexia groups (the non-cachexia group and cachexia group). We also calculated Spearman's rank correlation coefficients between each domain of the questionnaire for patients and ECOG PS groups (0–1, 2, 3 and 4), because advancing ECOG PS as well as cancer cachexia was associated with FAACT ACS.[11] Additionally, we calculated Pearson's correlation coefficients between matching domains in the ERD questionnaires for patients and family caregivers, because both questionnaires had domains on relationships between patients and family caregivers.

We developed short versions of the ERD questionnaires for patients and family caregivers. We selected one item for each

domain using the standard regression coefficient in the factor analysis and content representativeness as well as the clinical opinion. Cronbach's alpha and ICC in the short versions were calculated for internal consistency and test–retest reliability, respectively. Furthermore, concurrent validity and known-group validity were also examined.

Translation

The double-back translation method adapted from the EORTC Quality of Life Group Translation Procedure[30] was employed in this study.

Step 1: Forward translation

The developed Japanese version was translated into English by two professional translators who were native speakers of English. One of them was familiar with medical issues and the other was not, and they worked independently of each other to create two English versions for each ERD questionnaire.

Step 2: Reconciliation and integration

The two forward translations and the English version translated by the main researchers, including two native speakers of English, were reconciled and integrated into one tentative English version by one of the main researchers.

Step 3: Back translation

The tentative English version created through Step 2 was translated from English to Japanese by two professional translators who were native speakers of Japanese. Neither of them were familiar with medical issues, and they worked independently of each other to create two back translations for each ERD questionnaire.

Step 4: Review and discussion

The main researchers reviewed the original Japanese version and the two back translations and discussed the differences between them to reduce variability in the tentative English version through the expertise of the main researchers.

Step 5: Double-back translation

Based on the results of the review and discussions performed through Step 4, the tentative English version created through Step 2 was revised to create the final English version.We summarized the whole process of development of the ERD questionnaires for patients with advanced cancer and family caregivers in *Figure* 1.

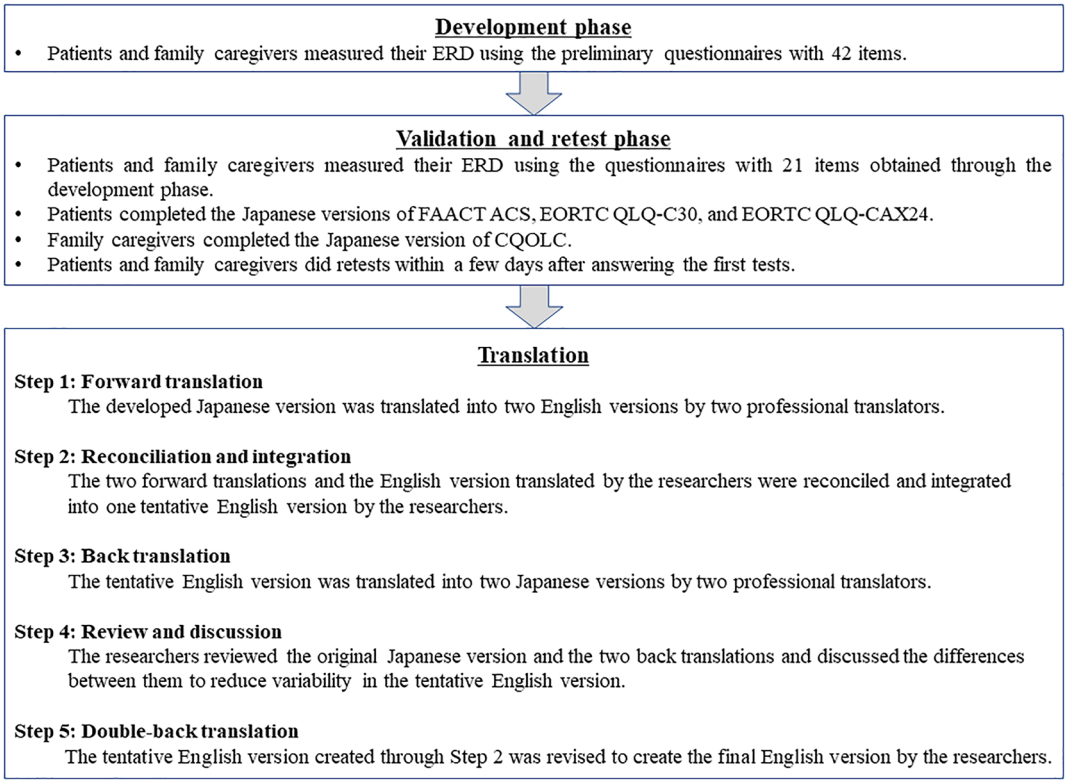

Figure 1 The process of development of the ERD questionnaires for patients with advanced cancer and family caregivers. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; EORTC QLQ-CAX24, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Cachexia 24; CQOLC, Caregiver Quality of Life Index-Cancer; ERD, eating-related distress; FAACT ACS, Functional Assessment of Anorexia/Cachexia Therapy Anorexia Cachexia Subscale.

Results

In the development phase, 162 pairs of patients and family caregivers were asked to complete the questionnaire, and 144 patients and 106 family caregivers responded (response rates, 88.9 and 65.4%, respectively). None of the respondents refused to participate. Three patients were excluded due to missing data for the exploratory factor analysis.

In the validation/retest phase, 333 pairs of patients and family caregivers were asked to complete the questionnaire, and 234 patients and 152 family caregivers responded (response rates, 70.3 and 45.6%, respectively). None of the respondents refused to participate. Overall, 183 patients and 112 family caregivers did the retest. Five patients and four family caregivers were excluded due to missing data for the exploratory factor analysis.

Participant characteristics

The characteristics of participants in both the development phase and validation/retest phase are summarized in *Table* 1. The population of the validation/retest phase was similar to that of the development-phase.

Regarding participants in the validation/retest phase, the mean age of patients was 61.8 ± 11.9 years, and the proportion of male patients was 50.9%. The proportion of patients with the primary cancer site in the lungs was 26.0%, the liver, biliary system and pancreas 15.4% and the upper and lower gastrointestinal tract 14.5%. The proportions of ECOG PS 1, 2 and 3 were 48.0, 19.7 and 20.6%, respectively. Almost 50% of patients had cancer cachexia. The mean score of Ingesta-VVAS was 6.1 ± 2.5. The proportions of palliative care settings were outpatient service 71.9%, hospital palliative care team 24.1% and palliative care unit 4.0%. The proportion of patients receiving chemotherapy was 66.8% followed by never treated/previous treatment (26.9%). The mean age of family caregivers was 58.4 ± 15.1 years, and the proportion of female family caregivers was 59.7%. The proportion of patients with a spouse or child was 77.0% and 13.7%, respectively.

Factor validity

The ERD questionnaire for patients with 21 items and the ERD questionnaire for family caregivers with 21 items obtained through the development phase were examined. There were no items with 20% or more of data missing or with a highly skewed distribution of ratings in both questionnaires.

Table 1 Participant characteristics

	Development phase	Validation and retest phase
Patients		
Number	144	234
Age in years	62.5 ± 12.8	61.8 ± 11.9
Sex		
Male	75 (52.4)	117 (50.9)
Female	68 (47.6)	113 (49.1)
Primary cancer site		
Lungs	28 (19.9)	59 (26.0)
Liver, biliary system and pancreas	27 (19.1)	35 (15.4)
Upper and lower gastrointestinal tract	19 (13.5)	33 (14.5)
Breast	11 (7.8)	16 (7.1)
Urinary system and prostate	7 (5.0)	14 (6.2)
Head and neck	6 (4.3)	9 (4.0)
Uterus and ovaries	13 (9.2)	8 (3.5)
Hematologic malignancy	3 (2.1)	8 (3.5)
Others	27 (19.1)	45 (19.8)
ECOG PS		
0	7 (4.9)	14 (6.3)
1	53 (37.3)	107 (48.0)
2	32 (22.5)	44 (19.7)
3	50 (35.2)	46 (20.6)
4	0 (0.0)	12 (5.4)
Body mass index (kg/m^2)	20.7 ± 3.6	21.6 ± 4.1
Cancer cachexia, yes	75 (54.0)	96 (46.8)
Weight loss in 1 month, yes	74 (56.5)	84 (39.4)
Symptomatic fluid retention, yes	29 (20.4)	52 (23.1)
Dietary intake[a]	5.5 ± 2.8	6.1 ± 2.5
Food type		
Normal food	-	189 (83.6)
Small amounts of solid food	-	29 (12.8)
Only liquids/nutritional supplements	-	8 (3.5)
Setting of care		
Outpatient service	105 (73.4)	164 (71.9)
Hospital palliative care team	34 (23.8)	55 (24.1)
Palliative care unit	4 (2.8)	9 (4.0)
Treatment status		
Pre-chemotherapy	10 (7.0)	14 (6.3)
Chemotherapy	90 (62.9)	149 (66.8)
Never treated/previous treatment	43 (30.1)	60 (26.9)
Family caregivers		
Number	106	152
Age in years	57.9 ± 14.3	58.4 ± 15.1
Sex		
Male	31 (29.5)	56 (40.3)
Female	74 (70.5)	83 (59.7)
Relationship to the patient		
Spouse	73 (68.9)	107 (77.0)
Child	15 (14.2)	19 (13.7)
Child-in-law	2 (1.9)	3 (2.2)
Parent	8 (7.5)	7 (5.0)
Sibling	6 (5.7)	2 (1.4)
Other	2 (1.9)	1 (0.7)

ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.
Values represent *n* (%) or mean ± SD where appropriate.
[a]Patients were asked to assess their dietary intakes with the Ingesta-Verbal/Visual Analogue Scale, which uses 10-point analogue scales (high scores indicate better dietary intakes).

Seven conceptual groups were extracted for the ERD among patients: (Patient (P) Factor 1) 'I cannot eat even though I want to eat more'; (P Factor 2) 'I do not understand the reason why I cannot eat'; (P Factor 3) 'I will become weaker if I cannot eat'; (P Factor 4) 'I have insufficient information about nutrients'; (P Factor 5) 'I have arguments with my family about food'; (P Factor 6) 'My appearance has changed a lot'; (P Factor 7) 'I spend less time talking with my family'. The cumulative proportion was 88.7% (*Table* 2).

Seven conceptual groups were extracted for the ERD among family caregivers: (Family caregiver (F) Factor 1) 'The patient cannot eat even though she/he wants to eat more'; (F Factor 2) 'I do not understand the reason why the patient cannot eat'; (F Factor 3) 'The patient will become weaker if she/he cannot eat'; (F Factor 4) 'I have insufficient information about nutrients'; (F Factor 5) 'I have arguments with the patient about food'; (F Factor 6) 'The appearance of the patient has changed a lot'; (F Factor 7) 'I spend less time talking with the patient'. The cumulative proportion was 88.5% (*Table* 3).

Table 2 Factor validity, internal consistency and test–retest reliability of ERD experienced by patients with advanced cancer: seven core domains

	Standardized regression coefficients							
	F1	F2	F3	F4	F5	F6	F7	Communality
1: I cannot eat even though I want to eat more (reduced dietary intake) (mean = 11.4, SD = 5.5, Cronbach's α = 0.90, ICC = 0.78)								
It is distressing that I get full quickly and cannot eat enough	0.07	0.01	−0.04	−0.02	**0.91**	0.00	0.00	0.84
It is distressing that I cannot enjoy eating	−0.04	−0.03	0.06	0.10	**0.90**	−0.04	0.01	0.85
It is distressing that I cannot eat even though I want to eat more	−0.03	0.09	−0.01	−0.04	**0.85**	0.10	−0.01	0.84
2: I do not understand the reason why I cannot eat (reasons why I cannot eat) (mean = 8.3, SD = 4.6, Cronbach's α = 0.94, ICC = 0.69)								
I do not understand the reason why I do not have an appetite	−0.01	**0.96**	0.00	0.03	0.03	−0.01	−0.02	0.95
I do not understand the reason why I cannot eat	0.01	**0.95**	0.00	0.01	0.03	−0.02	0.00	0.93
I do not understand the reason why I cannot eat enough	0.04	**0.88**	0.02	−0.04	−0.01	0.04	0.05	0.85
3: I will become weaker if I cannot eat (becoming weaker) (mean = 12.9, SD = 5.6, Cronbach's α = 0.95, ICC = 0.72)								
I am concerned that I will lose muscle strength if I cannot eat	−0.04	0.01	0.01	0.04	−0.02	**1.00**	−0.04	0.96
I am concerned that I will become weaker if I cannot eat	−0.01	0.01	0.02	0.02	−0.01	**0.95**	0.02	0.94
I am concerned that I will lose weight if I cannot eat	0.17	−0.01	0.02	−0.07	0.13	**0.74**	0.04	0.85
4: I have insufficient information about nutrients (insufficient information) (mean = 11.3, SD = 5.1, Cronbach's α = 0.96, ICC = 0.67)								
I have insufficient information about which nutrients I should avoid	0.00	0.03	**1.00**	−0.01	−0.01	−0.06	0.00	0.95
I have insufficient information about which nutrients I should prioritized	0.01	0.04	**0.93**	0.01	−0.01	0.05	−0.04	0.93
I have insufficient information about which nutritional supplements I should take	0.02	−0.05	**0.90**	0.00	0.03	0.07	0.05	0.91
5: I have arguments with my family about food (arguments with my family) (mean = 7.0, SD = 4.1, Cronbach's α = 0.87, ICC = 0.74)								
I have arguments with my family about food	0.01	0.01	−0.05	−0.01	−0.04	0.00	**0.98**	0.91
I get frustrated with my family over food	0.07	−0.07	−0.02	0.02	0.02	0.00	**0.92**	0.87
I am troubled that my family seems to try to force me to eat	−0.09	0.16	0.12	0.03	0.03	−0.01	**0.71**	0.69
6: My appearance has changed a lot (change in appearance) (mean = 10.6, SD = 5.3, Cronbach's α = 0.95, ICC = 0.83)								
It's hard for me to be seen by others as so skinny	**0.96**	0.00	0.05	−0.02	0.00	−0.04	0.01	0.92
It's hard for me that my appearance had changed a lot from before as I became thin	**0.94**	0.07	−0.07	0.04	−0.06	0.02	0.03	0.91
It's hard to see myself as so skinny	**0.89**	−0.05	0.06	0.01	0.06	0.05	−0.03	0.89
7: I spend less time talking with my family (time with my family) (mean = 8.9, SD = 5.2, Cronbach's α = 0.92, ICC = 0.70)								
I spend less time in daily life with my family because I cannot eat	−0.02	0.08	−0.01	**0.94**	−0.01	−0.02	−0.02	0.89
I spend less time talking with my family because I do not eat with them	0.03	−0.01	0.07	**0.94**	−0.11	0.03	0.02	0.89
I spend less time enjoying with my family during meals	0.01	−0.07	−0.07	**0.86**	0.18	0.01	0.02	0.85
Cumulative proportion, 88.7%								

Cronbach's α, Cronbach's alpha coefficient; ERD, eating-related distress; F#, Factors 1–7; ICC, intraclass correlation coefficient; SD, standard deviation.
Boldfaced numbers indicate attributes belonging to each domain.

Table 3 Factor validity, internal consistency and test–retest reliability of ERD experienced by family caregivers of patients with advanced cancer: seven core domains

	Standardized regression coefficients							
	F1	F2	F3	F4	F5	F6	F7	Communality
1: The patient cannot eat even though he/she wants to eat more (reduced dietary intake) (mean = 13.4, SD = 5.9, Cronbach's α = 0.96, ICC = 0.84)								
It is distressing to me that the patient cannot eat even though he/she wants to eat more	**0.96**	0.02	−0.02	0.01	0.02	−0.02	0.01	0.92
It is distressing to me that the patient cannot enjoy eating	**0.92**	0.02	0.07	−0.02	−0.02	0.05	−0.02	0.94
It is distressing to me that the patient gets full quickly and cannot eat enough	**0.86**	−0.02	0.03	0.16	−0.02	−0.06	0.03	0.87
2: I do not understand the reason why the patient cannot eat (reasons why the patient cannot eat) (mean = 8.5, SD = 5.1, Cronbach's α = 0.96, ICC = 0.67)								
I do not understand the reason why the patient does not have an appetite	0.04	0.02	0.01	**0.99**	0.01	−0.04	−0.06	0.96
I do not understand the reason why the patient cannot eat	0.09	−0.04	−0.01	**0.91**	0.00	0.03	0.03	0.93
I do not understand the reason why the patient cannot eat enough	−0.03	0.04	0.04	**0.85**	0.03	0.07	0.06	0.87
3: The patient will become weaker if he/she cannot eat (becoming weaker) (mean = 15.9, SD = 4.9, Cronbach's α = 0.96, ICC = 0.71)								
I am concerned that the patient will lose weight if he/she cannot eat	0.00	−0.08	**0.95**	0.00	0.07	0.00	0.07	0.91
I am concerned that the patient will lose muscle strength if he/she cannot eat	0.05	0.03	**0.93**	0.04	0.02	0.00	−0.08	0.91
I am concerned that the patient will become weaker if he/she cannot eat	0.02	0.09	**0.90**	0.00	−0.01	−0.05	0.03	0.92
4: I have insufficient information about nutrients (insufficient information) (mean = 13.4, SD = 4.8, Cronbach's α = 0.96, ICC = 0.63)								
I have insufficient information about which nutrients the patient should prioritize	0.00	**0.98**	−0.07	0.01	0.04	0.00	0.01	0.93
I have insufficient information about which nutritional supplements the patient should take	−0.02	**0.95**	0.04	−0.04	0.01	0.00	0.03	0.93
I have insufficient information about which nutrients the patient should avoid	0.03	**0.93**	0.05	0.04	−0.01	−0.01	−0.02	0.94
5: I have arguments with the patient about food (arguments with the patient) (mean = 8.8, SD = 4.6, Cronbach's α = 0.84, ICC = 0.79)								
I have arguments with the patient about food	−0.01	−0.08	−0.06	0.00	0.05	**0.96**	0.02	0.90
I get frustrated with the patient over food	−0.05	0.04	−0.03	0.02	0.07	**0.95**	−0.04	0.89
I am worried that I am forcing the patient to eat	0.19	0.11	0.23	0.04	−0.19	**0.58**	0.03	0.74
6: The appearance of the patient has changed a lot (change in appearance) (mean = 12.1, SD = 4.5., Cronbach's α = 0.84, ICC = 0.74)								
It's hard for me to see that the appearance of the patient had changed a lot from before as he/she became thin	0.01	0.00	0.04	−0.07	0.10	−0.04	**0.91**	0.85
It's hard for me that others see the patient as so skinny	−0.06	−0.02	−0.13	0.25	0.04	0.02	**0.82**	0.79
It's hard to see the patient as so skinny	0.12	0.05	0.17	−0.10	−0.11	0.03	**0.77**	0.80
7: I spend less time talking with the patient (time with the patient) (mean = 8.4, SD = 4.4, Cronbach's α = 0.86, ICC = 0.77)								
I spend less time talking with the patient because he/she does not eat with us	−0.07	0.03	0.00	0.02	**0.96**	−0.01	0.03	0.93

(*Continues*)

Table 3 (continued)

	Standardized regression coefficients							Communality
	F1	F2	F3	F4	F5	F6	F7	
I spend less time in daily life with the patient because he/she cannot eat	−0.08	0.03	0.06	0.08	**0.91**	0.02	−0.02	0.89
I spend less time enjoying with the patient during meals	0.49	−0.04	−0.01	−0.12	**0.66**	0.05	0.02	0.75
Cumulative proportion, 88.5%								

Cronbach's α, Cronbach's alpha coefficient; ERD, eating-related distress; F#, Factors 1–7; ICC, intraclass correlation coefficient; SD, standard deviation.
Boldfaced numbers indicate attributes belonging to each domain.

Concurrent validity

Pearson's correlation coefficients between the ERD questionnaire for patients and FAACT ACS, EORTC QLQ-C30 and EORTC QLQ-CAX24 are shown in *Table* 4. The scores of P Factors 1, 2, 3, 4, 5, 6 and 7 correlated with FAACT ACS (r = −0.63, −0.43, −0.55, −0.40, −0.38, −0.54 and −0.38, respectively). They correlated with FAACT ACS five-item anorexia symptoms (r = −0.63, −0.45, −0.47, −0.35, −0.37, −0.42 and −0.35, respectively) and FAACT ACS four-item anorexia concerns (r = −0.41, −0.32, −0.51, −0.33, −0.36, −0.60 and −0.34, respectively). They also correlated with EORTC QLQ-C30 Appetite loss (r = 0.56, 0.38, 0.44, 0.25, 0.24, 0.33 and 0.33, respectively) and EORTC QLQ-CAX24 (r = 0.58, 0.40, 0.60, 0.49, 0.38, 0.59 and 0.42, respectively). Furthermore, the total score across all factors of patients correlated with FAACT ACS, FAACT ACS five-item anorexia symptoms, FAACT ACS four-item anorexia concerns and EORTC QLQ-CAX24 (r = −0.64, −0.59, −0.54 and 0.71 respectively), whereas the total score of the short version of patients correlated with FAACT ACS, FAACT ACS five-item anorexia symptoms, FAACT ACS four-item anorexia concerns and EORTC QLQ-CAX24 (r = −0.60, −0.55, −0.53 and 0.68 respectively).

Pearson's correlation coefficients between the ERD questionnaire for family caregivers and CQOLC are shown in *Table* 5. The scores of F Factors 1, 2, 3, 4, 5, 6 and 7 correlated with the total score of CQOLC (r = −0.34, −0.30, −0.37, −0.37, −0.46, −0.42 and −0.40, respectively). The total score across all factors and that of the short version of family caregivers correlated with the total score of CQOLC (r = −0.52 and −0.51, respectively).

Internal consistency and test–retest reliability

The internal consistency (Cronbach's alpha) and test–retest reliability (ICC) are shown in *Tables* 2 and 3. The values of Cronbach's alpha and ICC of 7 factors of the ERD questionnaire for patients ranged from 0.87 to 0.96 and 0.67 to 0.83, respectively (*Table* 2). The values of Cronbach's alpha and ICC of all factors were 0.84 and 0.82, respectively. The values of Cronbach's alpha and ICC of the short version were 0.79 and 0.82, respectively.

The values of Cronbach's alpha and ICC of 7 factors of the ERD questionnaire for family caregivers ranged from 0.84 to 0.96 and 0.63 to 0.84, respectively (*Table* 3). The values of Cronbach's alpha and ICC of all factors were 0.84 and 0.80, respectively. The values of Cronbach's alpha and ICC of the short version were 0.77 and 0.79, respectively.

Known-group validity

Known-group validity between patient factors and family caregiver factors and cancer cachexia is shown in *Table* 6.

Table 4 Concurrent validity with each factor of the ERD questionnaire for patients

	P Factor 1: Reduced dietary intake	P Factor 2: Reasons why I cannot eat	P Factor 3: Becoming weaker	P Factor 4: Insufficient information	P Factor 5: Arguments with my family	P Factor 6: Change in appearance	P Factor 7: Time with my family	All factors of patients	Short version of patients
FAACT ACS	−0.63*	−0.43*	−0.55*	−0.40*	−0.38*	−0.54*	−0.38*	−0.64*	−0.60*
FAACT ACS five-item anorexia symptoms	−0.63*	−0.45*	−0.47*	−0.35*	−0.37*	−0.42*	−0.35*	−0.59*	−0.55*
FAACT ACS four-item anorexia concerns	−0.41*	−0.32*	−0.51*	−0.33*	−0.36*	−0.60*	−0.34*	−0.54*	−0.53*
EORTC QLQ-C30, Global health status	−0.43*	−0.16***	−0.31*	−0.29*	−0.16***	−0.23**	−0.27*	−0.39*	−0.37*
EORTC QLQ-C30, Physical functioning	0.31*	0.13	0.30*	0.11	0.18**	0.26*	0.24*	0.33*	0.33*
EORTC QLQ-C30, Role functioning	0.33*	0.07	0.24*	0.12	0.07	0.18**	0.26*	0.26*	0.25*
EORTC QLQ-C30, Emotional functioning	0.33*	0.18**	0.36*	0.26*	0.14***	0.35*	0.15***	0.36*	0.35*
EORTC QLQ-C30, Cognitive functioning	0.28*	0.13	0.24*	0.13	0.16***	0.17***	0.22**	0.30*	0.29*
EORTC QLQ-C30, Social functioning	0.28*	0.12	0.27*	0.21**	0.09	0.22**	0.18**	0.29*	0.29*
EORTC QLQ-C30, Fatigue	0.42*	0.14***	0.40*	0.20**	0.12	0.32*	0.26*	0.40*	0.40*
EORTC QLQ-C30, Nausea and vomiting	0.42*	0.20**	0.17**	0.18**	0.15***	0.25*	0.26*	0.34*	0.31*
EORTC QLQ-C30, Pain	0.28*	0.09	0.21**	0.09	0.17***	0.08	0.15***	0.24*	0.23*
EORTC QLQ-C30, Dyspnoea	0.35*	0.19**	0.24*	0.18**	0.18**	0.18**	0.25*	0.32*	0.32*
EORTC QLQ-C30, Sleep disturbance	0.14***	0.04	0.19**	0.11	0.12	0.15***	0.17***	0.20**	0.18**
EORTC QLQ-C30, Appetite loss	0.56*	0.38*	0.44*	0.25*	0.24*	0.33*	0.33*	0.52*	0.49*
EORTC QLQ-C30, Constipation	0.11	0.08	0.10	0.01	0.13	0.08	0.12	0.13***	0.14***
EORTC QLQ-C30, Diarrhoea	0.12	0.11	0.20**	0.07	0.11	0.19**	0.10	0.19**	0.17***
EORTC QLQ-C30, Financial difficulties	0.23**	0.15***	0.25*	0.24*	0.11	0.23**	0.11	0.28*	0.28*
EORTC QLQ-CAX24	0.58*	0.40*	0.60*	0.49*	0.38*	0.59*	0.42*	0.71*	0.68*

ERD, eating-related distress; P Factor #, Patient Factors 1–7.
Values represent Pearson's correlation coefficients.
*$P < 0.001$.
**$P < 0.01$.
***$P < 0.05$.

Table 5 Concurrent validity with each factor of the ERD questionnaire for family caregivers

	F Factor 1: Reduced dietary intake	F Factor 2: Reasons why the patient cannot eat	F Factor 3: Becoming weaker	F Factor 4: Insufficient information	F Factor 5: Arguments with the patient	F Factor 6: Change in appearance	F Factor 7: Time with the patient	All factors of family caregivers	Short version of family caregivers
CQOLC, Psychological burden	−0.36*	−0.25**	−0.42*	−0.37*	−0.37*	−0.42*	−0.33*	−0.49*	−0.47*
CQLQC, Positive emotions	−0.13	0.01	−0.15	0.00	−0.19***	−0.02	0.13	−0.08	−0.04
CQLQC, Financial burden	−0.12	−0.19***	−0.11	−0.30*	−0.14	−0.23**	−0.26**	−0.26**	−0.27**
CQLQC, Disruption of daily living	−0.21***	−0.32*	−0.19***	−0.25**	−0.48*	−0.34*	−0.51*	−0.44*	−0.47*
CQLQC, Total score	−0.34*	−0.30**	−0.37*	−0.37*	−0.46*	−0.42*	−0.40*	−0.52*	−0.51*

ERD, eating-related distress; F Factor #, Family caregiver Factors 1–7.
Values represent Pearson's correlation coefficients.
*$P < 0.001$.
**$P < 0.01$.
***$P < 0.05$.

Table 6 Known-group validity between patient factors and family caregiver factors and cancer cachexia

	Non-cachexia group (n = 108)		Cachexia group (n = 96)		
Patients	Mean	SD	Mean	SD	P
P Factor 1: Reduced dietary intake	10.5	5.4	12.1	5.4	0.046
P Factor 2: Reasons why I cannot eat	7.4	4.2	8.9	4.8	0.021
P Factor 3: Becoming weaker	11.4	5.5	14.6	5.2	<0.001
P Factor 4: Insufficient information	10.3	4.9	12.2	4.9	0.006
P Factor 5: Arguments with my family	6.2	4.1	7.8	4.1	0.001
P Factor 6: Change in appearance	9.1	5.2	12.4	5.2	<0.001
P Factor 7: Time with my family	8.4	5.4	9.8	5.0	0.015
All factors of patients	63.2	24.7	77.7	25.5	<0.001
Short version of patients	21.1	8.3	25.6	8.5	<0.001
	Non-cachexia group (n = 73)		Cachexia group (n = 57)		
Family caregivers	Mean	SD	Mean	SD	P
F Factor 1: Reduced dietary intake	11.9	6.0	14.8	5.9	0.006
F Factor 2: Reasons why the patient cannot eat	7.9	4.9	8.6	5.4	0.48
F Factor 3: Becoming weaker	13.9	5.4	18.1	3.7	<0.001
F Factor 4: Insufficient information	13.0	5.0	14.0	4.5	0.35
F Factor 5: Arguments with the patient	8.5	5.1	8.9	4.2	0.32
F Factor 6: Change in appearance	10.2	4.5	13.9	3.9	<0.001
F Factor 7: Time with the patient	7.6	4.4	8.8	4.3	0.08
All factors of family caregivers	73.1	26.3	87.1	21.8	0.002
Short version of family caregivers	24.2	8.5	27.7	7.5	0.026

F Factor #, Family caregiver Factors 7; P Factor #, Patient Factors 1–7; SD, standard deviation.
The Mann–Whitney U test was performed.

The cachexia group had significantly higher scores than the non-cachexia group for each factor, all factors and the short version of the ERD questionnaire for patients. The cachexia group had significantly higher scores than the non-cachexia group for three factors, all factors and the short version of the ERD questionnaire for family caregivers.

Spearman's rank correlation coefficients between each factor, all factors and the short version of the ERD questionnaire for patients and ECOG PS groups (0–1, 2, 3 and 4) are shown in *Table* S1. The scores for each factor, all factors and the short version significantly increased with increases in ECOG PS.

Correlations between factors for patients and family caregivers

Pearson's correlation coefficients between matching factors in the questionnaires for patients and family caregivers are shown in *Table* 7. Factors 1, 5, 6 and 7 of patients correlated

Table 7 Correlations between factors of ERD questionnaires for patients and family caregivers

	P Factor 1: Reduced dietary intake	P Factor 2: Reasons why I cannot eat	P Factor 3: Becoming weaker	P Factor 4: Insufficient information	P Factor 5: Arguments with my family	P Factor 6: Change in appearance	P Factor 7: Time with my family	All factors of family caregivers	Short version of family caregivers
F Factor 1: Reduced dietary intake	0.51*	0.42*	0.33*	0.43*	0.32*	0.39*	0.35*	0.53*	0.50*
F Factor 2: Reasons why the patient cannot eat	0.08	0.30*	−0.07	0.28**	0.31*	0.12	0.33*	0.22**	0.25**
F Factor 3: Becoming weaker	0.30*	0.25**	0.29**	0.34*	0.31*	0.35*	0.31*	0.42*	0.40*
F Factor 4: Insufficient information	0.14	0.16	0.00	0.31*	0.18***	0.15	0.28**	0.25**	0.26**
F Factor 5: Arguments with the patient	0.11	0.35*	0.11	0.30*	0.53*	0.20***	0.29**	0.31*	0.34*
F Factor 6: Change in appearance	0.20***	0.27**	0.23**	0.38*	0.35*	0.41*	0.32*	0.41*	0.41*
F Factor 7: Time with the patient	0.27**	0.33*	0.04	0.24**	0.38*	0.19***	0.41*	0.37*	0.40*
All factors of patients	0.33*	0.42*	0.19***	0.46*	0.48*	0.37*	0.46*	0.51*	0.51*
Short version of patients	0.33*	0.45*	0.16	0.44*	0.47*	0.34*	0.43*	0.49*	0.51*

F Factor #, Family caregiver Factors 1–7; P Factor #, Patient Factors 1–7.
Values represent Pearson's correlation coefficients.
*$P < 0.001$.
**$P < 0.01$.
***$P < 0.05$.

with those of family caregivers (r = 0.51, 0.53, 0.41 and 0.41, respectively). All factors and the short version of patients also correlated with those of family caregivers (r = 0.51 and 0.51, respectively).

Discussion

We validated the newly developed tools that measure ERD experienced by patients with advanced cancer and family caregivers. ERD is an important problem to address in patients and their family caregivers because it can adversely affect QOL. It is not adequately measured by other tools. In addition, the questionnaire for family caregivers of patients with cancer cachexia is the first of its kind in the world.

Seven factors were extracted by the exploratory factor analysis of each ERD questionnaire for patients and family caregivers. Seven conceptual groups for patients and family caregivers matched each other. Regarding factors extracted in the ERD questionnaire for patients, (P Factor 1) 'I cannot eat even though I want to eat more', (P Factor 3) 'I will become weaker if I cannot eat' and (P Factor 6) 'My appearance has changed a lot' were already included in FAACT ACS and EORTC QLQ-CAX24. However, (P Factor 2) 'I do not understand the reason why I cannot eat', (P Factor 4) 'I have insufficient information about nutrients', (P Factor 5) 'I have arguments with my family about food' and (P Factor 7) 'I spend less time talking with my family' appeared to be new conceptual groups.

Overall concurrent validity between the ERD questionnaire for patients and FAACT ACS and EORTC QLQ-CAX24 were moderate. This may be because they have been developed to measure different things—ERD and QOL. ERD is only one of many symptoms and other problems that affect QOL in cachexia. The values of concurrent validity in P Factors 2, 4, 5 and 7 were weak, whereas those in P Factors 1, 3 and 6 were moderate. These results supported FAACT ACS and EORTC QLQ-CAX24 not containing P Factor 2, 4, 5 or 7. On the other hand, overall concurrent validity between the ERD questionnaire for family caregivers and CQOLC, which was developed to measure the QOL of the family caregivers of patients with cancer, was weak to moderate. This may be because the correlations between the physical symptoms of patients and CQOLC were weak.[27,28]

Regarding internal consistency, the values of Cronbach's alpha were high in both ERD questionnaires for patients and family caregivers. This may be because this study consisted of the development phase and validation/retest phase. Concerning test–retest reliability, the values of ICC were also high in both ERD questionnaires. This may be because retests were done within a week after the first tests.

The most useful result obtained is related to known-group validity between the ERD questionnaire for patients and can-

cer cachexia and ECOG PS. Each factor, all factors and the short version appear to consistently be able to measure an aspect of cachexia-related QOL of patients. Furthermore, all factors and the short version of the ERD questionnaire for family caregivers also appear to be able to measure an aspect of cachexia-related QOL of family caregivers.

Regarding correlations between matching factors in patients and family caregivers, moderate and weak correlations were observed for Factors 5 and 7, which represent relationships between patients and family caregivers, respectively. In addition, all factors and the short version of patients also moderately correlated with those of family caregivers. These results indicate that cancer anorexia and cachexia not only cause distress for patients and family caregivers but also affect their relationships.

There are multiple strengths of this study, including the team of investigators, a strong track record of prior publications focused on ERD, the inclusion of family caregivers, the number of participants, methodology, comparison to validated patient-reported outcomes, detailed translation process to English and inclusion of >70% patients in the outpatient setting with 67% receiving cancer-directed therapy.

However, this study has several limitations that need to be addressed. The response rate of family caregivers in the validation/retest-phase was low due to the prohibition of visits to patients in hospitals. Or patients were recruited at clinic when their family caregivers were not in attendance under the tight restrictions due to the COVID-19 pandemic. However, this is not a fatal flaw because the objective of the study was to develop and validate tools, not survey the actual severity of ERD experienced by patients and family caregivers. Moreover, because this study was conducted in one country, the results obtained may not be generalizable to other countries. All patients included in the study had adequate access to food; however, access to food can be a significant contributor to ERD in some countries. Therefore, further studies for cultural validation are warranted in the near future. Furthermore, because this study was a cross-sectional analysis of a questionnaire, survival data were not obtained. However, as many patients who were in good performance status and received chemotherapy were included, the tools seem to be useful in earlier stages of disease with longer survival times. The ERD questionnaire for patients has dimensions that pertain to subjects who live and eat with their family caregivers. When the tools are used in subjects who are alone or who are inpatients and do not interact with their family caregivers during meals, a subscale score without items on relationships with family caregivers can be independently evaluated. Additionally, although Japanese patients and family caregivers are likely to depend on parenteral nutrition and hydration,[26,31] there are no data on whether implementation of parenteral nutrition and hydration can alleviate ERD among patients and family caregivers.

We intend to perform clinical trials with the aim of investigating the effects of new drugs stimulating appetite on the cachexia-related QOL of patients and family caregivers and the development of holistic multimodal interventions for patients with cancer cachexia and family caregivers. Both FAACT ACS and EORTC QLQ CAX24 measure QOL, but holistic multimodal interventions may target appetite and distress. To use the new ERD questionnaires is preferable if distress is an outcome of interest. However, the ERD questionnaires are not intended to be a symptom scale, and, therefore, they do not contain this domain.

We have already had Japanese versions and English versions of ERD questionnaires for patients and for family caregivers. Furthermore, we developed short versions, which are useful in daily clinical practice as well as in clinical trials. A reason for development of short versions is to reduce the patient burden of completing a patient-reported outcome measure. Minimizing burden of measures in clinical trials is important not just because of the benefit for patients but because it reduces the likelihood of missing data.

Conclusion

Newly developed tools that measure ERD experienced by patients with advanced cancer and family caregivers were validated. Short versions were also developed. The ERD questionnaire for patients can fill an important gap between actual cachexia-related distress among patients and existing patient-reported outcome measures of QOL in cachexia, including FAACT ACS and EORTC QLQ-CAX24. The ERD questionnaire for family caregivers is the first of its kind in the world. These tools can complement existing patient-reported outcome measures in future clinical trials.

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The authors of this manuscript certify that they comply with the ethical guidelines for editorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.[32]

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Conflict 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.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Appendix A

Questionnaire for Eating-Related Distress among Patients with advanced cancer (QERD-P)

Long version.

Please circle the number that best describes how you felt during the past 1 week.

1: strongly disagree, 2: disagree, 3: somewhat disagree, 4: neutral (neither agree nor disagree), 5: somewhat agree, 6: agree, 7: strongly agree.

Instructions

1. Sum individual items to obtain a subscale score, which can be independently evaluated.
2. When there are missing items, subscale scores can be prorated as long as two of the three items in each subscale were answered. This can be done by using the formula below: Prorated subscale score = [sum of the scores of two items] × 3/2.
3. Add subscale scores to derive a total score.
4. The higher the score, the higher the distress.
5. The questionnaire can be used by citing the paper on development and validation of the questionnaire.

	Patient							
1.1	**It is distressing that I cannot eat even though I want to eat more**	1	2	3	4	5	6	7
1.2	It is distressing that I cannot enjoy eating	1	2	3	4	5	6	7
1.3	It is distressing that I get full quickly and cannot eat enough	1	2	3	4	5	6	7
2.1	**I do not understand the reason why I cannot eat**	1	2	3	4	5	6	7
2.2	I do not understand the reason why I do not have an appetite	1	2	3	4	5	6	7
2.3	I do not understand the reason why I cannot eat enough	1	2	3	4	5	6	7
3.1	**I am concerned that I will become weaker if I cannot eat**	1	2	3	4	5	6	7
3.2	I am concerned that I will lose muscle strength if I cannot eat	1	2	3	4	5	6	7
3.3	I am concerned that I will lose weight if I cannot eat	1	2	3	4	5	6	7
4.1	**I have insufficient information about which nutrients I should prioritized**	1	2	3	4	5	6	7
4.2	I have insufficient information about which nutrients I should avoid	1	2	3	4	5	6	7
4.3	I have insufficient information about which nutritional supplements I should take	1	2	3	4	5	6	7
5.1	**I have arguments with my family about food**	1	2	3	4	5	6	7
5.2	I am troubled that my family seems to try to force me to eat	1	2	3	4	5	6	7
5.3	I get frustrated with my family over food	1	2	3	4	5	6	7
6.1	**It's hard for me that my appearance had changed a lot from before as I became thin**	1	2	3	4	5	6	7
6.2	It's hard for me to be seen by others as so skinny	1	2	3	4	5	6	7
6.3	It's hard to see myself as so skinny	1	2	3	4	5	6	7
7.1	**I spend less time talking with my family because I do not eat with them**	1	2	3	4	5	6	7
7.2	I spend less time enjoying with my family during meals	1	2	3	4	5	6	7
7.3	I spend less time in daily life with my family because I cannot eat	1	2	3	4	5	6	7

Boldfaced items indicate those belonging to the short version.

Questionnaire for Eating-Related Distress among Family caregivers of patients with advanced cancer (QERD-F)

Long version.

Please circle the number that best describes how you felt during the past 1 week.

1: strongly disagree, 2: disagree, 3: somewhat disagree, 4: neutral (neither agree nor disagree), 5: somewhat agree, 6: agree, 7: strongly agree.

Instructions

1. Sum individual items to obtain a subscale score, which can be independently evaluated.
2. When there are missing items, subscale scores can be prorated as long as two of the three items in each subscale were answered. This can be done by using the formula below: Prorated subscale score = [sum of the scores of two items] × 3/2.
3. Add subscale scores to derive a total score.
4. The higher the score, the higher the distress.
5. The questionnaire can be used by citing the paper on development and validation of the questionnaire.

	Family							
1.1	**It is distressing to me that the patient cannot eat even though she/he wants to eat more**	1	2	3	4	5	6	7
1.2	It is distressing to me that the patient cannot enjoy eating	1	2	3	4	5	6	7
1.3	It is distressing to me that the patient gets full quickly and cannot eat enough	1	2	3	4	5	6	7
2.1	**I do not understand the reason why the patient cannot eat**	1	2	3	4	5	6	7
2.2	I do not understand the reason why the patient does not have an appetite	1	2	3	4	5	6	7
2.3	I do not understand the reason why the patient cannot eat enough	1	2	3	4	5	6	7
3.1	**I am concerned that the patient will become weaker if she/he cannot eat**	1	2	3	4	5	6	7
3.2	I am concerned that the patient will lose muscle strength if she/he cannot eat	1	2	3	4	5	6	7
3.3	I am concerned that the patient will lose weight if she/he cannot eat	1	2	3	4	5	6	7
4.1	**I have insufficient information about which nutrients the patient should prioritize**	1	2	3	4	5	6	7
4.2	I have insufficient information about which nutrients the patient should avoid	1	2	3	4	5	6	7
4.3	I have insufficient information about which nutritional supplements the patient should take	1	2	3	4	5	6	7
5.1	**I have arguments with the patient about food**	1	2	3	4	5	6	7
5.2	I am worried that I am forcing the patient to eat	1	2	3	4	5	6	7
5.3	I get frustrated with the patient over food	1	2	3	4	5	6	7
6.1	**It's hard for me to see that the appearance of the patient had changed a lot from before as she/he became thin**	1	2	3	4	5	6	7
6.2	It's hard for me that others see the patient as so skinny	1	2	3	4	5	6	7
6.3	It's hard to see the patient as so skinny	1	2	3	4	5	6	7
7.1	**I spend less time talking with the patient because she/he does not eat with us**	1	2	3	4	5	6	7
7.2	I spend less time enjoying with the patient during meals	1	2	3	4	5	6	7
7.3	I spend less time in daily life with the patient because she/he cannot eat	1	2	3	4	5	6	7

Boldfaced items indicate those belonging to the short version.