Peer Review File

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Reviewer A

Comment 1:
Authors stated that the aim was to examine the associations between throat complications, namely deglutition difficulty (DD) and food bolus obstruction (FBO) and eating-related QOL. However, data analysis and results are not well aligned with the study aims. To my understanding, eating-related QOL was the outcome variable, with DD, FBO, socio-demographic and clinical variables as independent variables, which are in line with the study aims. Pls re-consider the aim of the study and revise data analysis/results if needed.

Reply 1

Thank you for the comment. We agree and have revised the following text. The newly included changes are in red font.
(see Page 3).

[Before revision]

ABSTRACT

Background: This study examined the effect of throat complications, namely, deglutition difficulty (DD) and food bolus obstruction (FBO), on eating-related quality of life (ER-QOL) in patients with cancer.

Methods: This study analyzed data from a self-reported questionnaire survey of patients with advanced cancer at 11 palliative care services. The inclusion criteria were: 1) new referrals to palliative care; 2) age ≥20 years; 3) locally advanced or metastatic cancer; 4) a known diagnosis of malignancy, and (5) ability to complete a self-reported questionnaire. DD and FBO were measured using the 11-point Numeric Rating Scale (NRS), whereas ER-QOL was assessed using the 12-item FAACT Anorexia/ Cachexia Subscale.

Results: Of the 495 patients invited to participate, 378 agreed (response rate 76.4%). After excluding patients with missing data, the data of 332 were analyzed; 26.5% had DD (NRS≥1) and 28.3% had FBO (NRS≥1). Multivariate analysis showed that DD and FBO were significantly associated with lower ER-QOL, independent of performance status and the presence of cancer cachexia, with coefficients of −6.34 (95% CI, −9.55 to −3.14) and −5.88 (95% CI, −8.68 to −3.09) for DD and FBO, respectively (all P<.001)

Conclusions: ER-QOL deteriorated as throat complications worsened; thus, healthcare providers need to pay attention to symptoms indicative of throat complications. Furthermore, to improve ER-QOL, DD and FBO need to be diagnosed and treated carefully.

[After revision]

ABSTRACT

Objectives: Swallowing disorders including difficulty swallowing and food bolus obstruction, result in reduced dietary intake—a common occurrence that leads to cachexia in patients with advanced cancer. This study examined the effects of swallowing difficulty and food bolus obstruction on cachexia-related quality of life (QOL).

Methods: This study secondarily analyzed data from a self-reported questionnaire survey of adult patients with advanced cancer at 11 palliative care services. Difficulty swallowing and food bolus obstruction were measured using the 11-point Numeric Rating Scale (NRS), whereas dietary intake and cachexia-related QOL were assessed using the Ingesta–Verbal/Visual Analog Scale and the Functional Assessment of Anorexia/Cachexia Therapy Anorexia/Cachexia Subscale. The multiple logistic regression model was used to identify factors associated with levels of difficulty swallowing and food bolus obstruction.

Results: Of the invited 495 patients, 378 agreed to participate (response rate 76.4%). After excluding participants with missing data, the data of 332 participants were analyzed; 26.5% had difficulty swallowing (NRS≥1) and 28.3% had food bolus obstruction (NRS≥1). Multivariate analysis showed that difficulty swallowing and food bolus obstruction were significantly associated with lower cachexia-related QOL, independent of performance status and the presence of cachexia, with coefficients of −6.34 (95% [confidence interval (CI)], −9.55 to −3.14, $P<0.001$) and −5.88 (95% CI, −8.68 to −3.09, $P<0.001$) for difficulty swallowing and food bolus obstruction, respectively.

Significance of Results: Cachexia-related QOL deteriorated as difficulty swallowing and food bolus obstruction worsened; thus, healthcare providers must diagnose and treat swallowing disorders in a timely manner to prevent progression of cachexia and improve cachexia-related QOL.

Comment 2:

Background information should include some descriptions/definitions/ of outcome variables and independent variables as well as a brief summary of the existing few studies having the same/similar study aims.

Reply 2

Thank you for the comment. We agree and have revised the following text. The newly included changes are in red font.

(see Page 5-6).

[Before revision]

INTRODUCTION

The sensation of solid food or liquids moving down the throat is integral to meal enjoyment, and swallowing cold, carbonated water relieves thirst (1). However, cancer progression causes dysphagia in many patients, including those with head and neck cancers (2), and patients with cancer and throat complications presumably experience ageusia (3). Thus, patients with advanced cancer and their families can suffer from eating-related distress. This complex entity encompasses patients' struggle to nourish themselves, emotional and social consequences of the inability to maintain food intake, and profound disturbance in family relationships (4). However, to the best of our knowledge, few studies have investigated the association between throat complications and eating-related quality of life (ER-QOL) in patients with advanced cancer receiving palliative care. This study aimed to explore the potential associations between throat complications – namely, deglutition difficulties and food bolus obstruction – and ER-QOL as well as with the dietary intake in patients with cancer. We present the following article in accordance with the STROBE reporting checklist.

[After revision]

INTRODUCTION

Cancer cachexia is a multifactorial syndrome involving the constant loss of skeletal muscle mass with or without fat mass loss that cannot be completely reversed by usual nutritional care and can lead to progressive functional impairment (1, 2). This occurs due to negative protein and energy imbalances resulting from a combination of reduced dietary intake, hypo-anabolism, and hyper-catabolism in systemic inflammation (1, 2). The prevalence of cachexia ranges from 50–80% in advanced cancer, and it can be considered the cause of death in 20–30% of cases (3). However, to date, there is no standard strategy for combating cancer cachexia despite its high frequency and negative impact on survival and quality of life (QOL) of patients with cancer (4,5).

In systemic inflammation, pro-inflammatory cytokines act through changes in the central nervous system, particularly the hypothalamic–pituitary–adrenal axis and sympathetic nervous system (6). Thus, exposure to pro-inflammatory cytokines in the central nervous system evokes anorexia and reduced dietary intake in patients with advanced cancer, although increasing dietary intake is a principal component of cancer cachexia management (6). In addition, patients frequently suffer from nutritional impact symptoms, which reduce dietary intake and promote weight loss, including pain, nausea and vomiting, taste and smell disturbances, drowsiness, and depression, leading to impaired physical function and deteriorated QOL (6-10).

An observational study conducted in patients with various types of advanced cancer in palliative care settings demonstrated that oral issues result in nutritional impact symptoms that in turn influence the physical, social, and psychological well-being of patients; therefore, such oral issues must be assessed in the early stages to prevent an inability to eat or drink (11). The study also showed a strong relationship between mucositis, dry mouth, and swallowing disorders (11). Among oral issues, difficulty swallowing and food bolus obstruction directly cause reduced dietary intake; these are commonly observed

symptoms that lead to cachexia in patients with advanced cancer (6-9). As some of these patients may benefit from oral care to mitigate nutritional impact symptoms and nutritional care to increase dietary intake, they must be provided with the opportunity to receive optimal care (12, 13).

In previous studies that measured QOL of patients with difficulty swallowing and food bolus obstruction, Swallowing QOL questionnaire (SWAL-QOL) and the Swallowing Quality of Care questionnaire (SWAL-CARE), which measure overall QOL, were the tools used (14-16). According to these studies, lower difficulty swallowing and food bolus obstruction were significantly associated with a better overall QOL. However, to the best of our knowledge, the associations of difficulty swallowing and food bolus obstruction with reduction in dietary intake and impaired QOL remain unknown among patients with advanced cancer in palliative care settings. Therefore, this study aimed to investigate the prevalence and severity of difficulty swallowing and food bolus obstruction and examine the effect of these symptoms on dietary intakes and cachexia-related QOL. We present the following article in accordance with the STROBE reporting checklist.

Comment 3:
DD and FBO was measured by VVAS. The scoring of the VVAS (e.g. 0-10) and cut-off points (0, 1-3, and >4) were not stated or justified.

Reply 3

Thank you for the comment. We agree and have revised the following text. The newly included changes are in red font.
(see Page 9, line 208).

[Before revision]

Statistical analysis

We classified throat complications (deglutition difficulty and food bolus obstruction) into three groups based on NRS scores of 0, 1–3, and ≥4.

[After revision]

Statistical analysis

We classified difficulty swallowing and food bolus obstruction into three levels for analysis based on previous research: NRS=0 was defined as none, NRS=1–3 as mild, and NRS ≥4 as moderate to severe (10).

Comment 4:
Eating-related QOL was measured by the 12-item FAACT A/CS. Unclear whether this was translated and validated in Japan. The 5-item anorexia symptom subscale and the 4-item anorexia concern subscale were used for data analysis. Wonder any rationale behind for using these 2 subscales from the FAACT A/CS.

Reply 4

Thank you for the comment. We agree and have revised the following text. The newly included changes are in red font.
We have included additional data to improve clarity (see Page 8, line 190).

[After revision]

These subscales have also been applied to evaluate the treatment effects of cachexia in patients with advanced cancer (21-24). The Japanese version of the FAACT ACS has been published by the developers (25).

Comment 5:
Data analysis part can be benefited from including a more clear descriptions after reconsidering the study aims.

Reply 5

Thank you for the comment. We agree and have revised the following text. The newly included changes are in red font.
(see Page 9, line 194).

[Before revision]

Statistical analysis

The primary endpoints were throat complications, namely, deglutition difficulties and food bolus obstruction, ER-QOL, and dietary intake. Patients with missing data related to the primary endpoints were excluded from the analysis. Patient demographics and clinical characteristics are presented as the number and percentage (%) for categorical variables and as mean with standard deviation (SD) for continuous variables, as appropriate. Cachexia was diagnosed based on the criteria from the international consensus: %WL in 6 months ≥5% or BMI <20 kg/m^2 + %WL in 6 months ≥2%. Patients with scores above or below these cutoff values were classified into a non-cachexia group or cachexia group, respectively (13).

To examine the impact of deglutition difficulty (NRS≥1) and food bolus obstruction (NRS≥1), we used independent-sample *t*-tests and analysis of variance (ANOVA) to identify variables that were

considered potential confounders, including sex, age, primary cancer site, ECOG-PS, treatment status (pre-chemotherapy, chemotherapy, and never treated/previously treated), and cachexia (non-cachexia vs. cachexia). We classified throat complications (deglutition difficulty and food bolus obstruction) into three groups based on NRS scores of 0, 1–3, and ≥4. To investigate the relationships between deglutition difficulty, food bolus obstruction, and dietary intake, we performed independent-sample *t*-tests and ANOVA to compare the 12-item FAACT A/CS, 5-item anorexia symptoms, and 4-item anorexia concerns among the three patient subgroups.

To assess the effects of deglutition difficulty and food bolus obstruction on the 12-item FAACT A/CS score and dietary intake, a crude estimation was performed using a robust linear model. The multivariate model was adjusted for sex, age (two age groups: <69 and ≥70 years), primary cancer site, ECOG-PS (two groups: PS 0–2 and PS 3–4), treatment status (pre-chemotherapy, chemotherapy, and never treated/previously treated), and cachexia (non-cachexia vs. cachexia). All results with a *P*-value <0.05 were considered significant. All statistical analyses were performed using SPSS (version 28.0.1, IBM Corp., Armonk, NY, USA, USA) and EZR (Saitama Medical Center, Jichi Medical University) (14).

[After revision]

Statistical analysis

The primary endpoints were difficulty swallowing, food bolus obstruction, dietary intake, and the FAACT ACS. We excluded patients with missing data related to the primary endpoint from the analysis. Patient demographics and clinical characteristics are presented as number (%) for categorical variables and mean (standard deviation [SD]) for continuous variables, where appropriate. Cachexia was defined as a %WL over the previous 6 months ≥5% or BMI <20 kg/m^2 + %WL over the previous 6 months ≥2%, based on international consensus criteria (1).

To examine the impact of difficulty swallowing (NRS ≥1) and food bolus obstruction (NRS ≥1), we used independent-sample t-tests and analysis of variance (ANOVAs) to explore potential confounding variables such as sex, age, primary cancer site, ECOG PS, anticancer treatment status (pre-chemotherapy, chemotherapy, and never treated/previously treated), and cachexia (non-cachexia and cachexia).

We classified difficulty swallowing and food bolus obstruction into three levels for analysis based on previous research: NRS=0 was defined as none, NRS=1–3 as mild, and NRS ≥4 as moderate to severe (10). Independent-samples t-tests and ANOVAs were used to investigate the relationships among difficulty swallowing (three groups), food bolus obstruction (three groups), dietary intake, FAACT ACS 12-item, 5-item anorexia symptoms scores, and 4-item anorexia concerns scores (24).

To assess the effects of dietary intake and FAACT ACS 12-item on difficulty swallowing and food bolus obstruction, we developed a robust linear model with crude estimation. Variables with significant

differences were included in the multiple logistic regression model as independent variables. The multiple logistic regression model was used to identify factors associated with levels of difficulty swallowing and food bolus obstruction. The dependent variable was difficulty swallowing and food bolus obstruction status, which was classified into categories of "none," "mild," and "moderate to severe" levels of difficulty swallowing and food bolus obstruction. A multivariate model adjusted for sex, age (two groups: <69 years and ≥70 years), primary cancer site, ECOG PS (two groups: PS: 0–2 and PS: 3–4), treatment status (pre-chemotherapy, chemotherapy, and never treated/previously treated), and cachexia (non-cachexia and cachexia) was generated. Significance was set at P <0.05. All analyses were performed using SPSS version 28.0.1 (IBM Corp., Armonk, NY, USA) and EZR (Saitama Medical Center, Jichi Medical University) (26).

Comment 6:
Results: the same comments above.
Data analysis part can be benefited from including a more clear descriptions after reconsidering the study aims.

Reply 6

Thank you for the comment. We agree and have revised the following text. The newly included changes are in red font.
(see Page 10, line 229).

[Before revision]

RESULTS

Of the 495 patients invited to participate in the study, 378 (76.4%) completed the questionnaire; none of the patients refused to participate. Forty-six patients were excluded from analysis owing to missing data related to the primary endpoints. Therefore, the data of 332 patients were analyzed. The patient demographics and clinical characteristics are summarized in Table 1. In this study cohort, the proportion of male patients was 51.5%, and the mean age was 61.6±12.1 years. The proportion of patients with the primary cancer site located in the upper/lower gastrointestinal tract, liver/biliary system/pancreas, and lung was 13.9%, 17.2%, and 22.6%, respectively. The proportion of patients with ECOG-PS 0–2 and 3–4 was 71.9% and 26.8%, respectively. The proportion of patients who were receiving chemotherapy and those who were never treated or previously treated was 65.4% and 26.8%, respectively. Moreover, 46.7% of patients had cachexia.

Prevalence and factors associated with difficulty swallowing and food bolus obstruction

The prevalence of throat complications, namely, difficulty swallowing and food bolus obstruction, is shown in Table 2. Among patients with advanced cancer who were receiving palliative care, 26.5% and

28.3% had deglutition difficulty (NRS≥1) and food bolus obstruction (NRS≥1), respectively. Male sex (deglutition difficulty, *P*=.027); age >70 years (deglutition difficulty, *P*=.037; and food bolus obstruction, *P*=.049); head and neck organs as the primary cancer site (deglutition difficulty, *P*<.001; food bolus obstruction, *P*=.026); ECOG-PS 3–4 (deglutition difficulty, *P*=.019; food bolus obstruction, *P*=.01); and ongoing or completed treatment (deglutition difficulty, *P*=.017; food bolus obstruction, *P*=.007) were associated with deglutition difficulty and food bolus obstruction (both NRS≥1).

Association among throat complications, dietary intake, and the ER-QOL

The relationships of deglutition difficulty and food bolus obstruction with dietary intake, 12-item FAACT A/CS, 5-item anorexia symptoms, and 4-item anorexia concerns are summarized in Table 3. Greater deglutition difficulty and food bolus obstruction were significantly associated with lower dietary intake (according to the Ingesta-VVAS) and worse ER-QOL (assessed by 12-item FAACT A/CS, 5-item anorexia symptoms, and 4-item anorexia concerns). Multivariate analysis revealed that deglutition difficulty and food bolus obstruction; ECOG-PS 3–4; and cachexia were associated with dietary intake and the 12-item FAACT A/CS score (Table 4 and 5).

[After revision]

RESULTS

Of the 495 patients invited to participate in the study, 378 (76.4%) completed the questionnaire; none of the patients refused to participate. Forty-six patients were excluded from analysis owing to missing data related to the primary endpoints. Therefore, the data of 332 patients were analyzed.

The patient demographics and clinical characteristics

The patient demographics and clinical characteristics are summarized in Table 1. In this study cohort, the proportion of male patients was 51.5%, and the mean age was 61.6±12.1 years. The proportion of patients with the primary cancer site located in the upper/lower gastrointestinal tract, liver/biliary system/pancreas, and lung was 13.9%, 17.2%, and 22.6%, respectively. The proportion of patients with ECOG-PS 0–2 and 3–4 was 71.9% and 26.8%, respectively. The proportion of patients who were receiving chemotherapy and those who were never treated or previously treated was 65.4% and 26.8%, respectively. Moreover, 46.7% of patients had cachexia.

Prevalence and factors associated with dysphagia and food bolus obstruction

The prevalence of swallowing disorders, namely, difficulty swallowing and food bolus obstruction, are shown in Table 2. Among patients with advanced cancer who were receiving palliative care, 26.5% and 28.3% had difficulty swallowing (NRS≥1) and food bolus obstruction (NRS≥1), respectively. Male sex (difficulty swallowing, *P*=0.027); age >70 years (difficulty swallowing, *P*=0.037; and food bolus obstruction, *P*=0.049); head and neck organs as the primary cancer site (difficulty swallowing, *P*<0.001; food bolus obstruction, *P*=0.026); ECOG-PS 3–4 (difficulty swallowing, *P*=0.019; food bolus obstruction, *P*=0.01); and ongoing or completed treatment (difficulty swallowing, *P*=0.017; food bolus

obstruction, *P*=0.007) were associated with difficulty swallowing and food bolus obstruction (both NRS≥1).

Association between swallowing disorders with dietary intake and cachexia-related QOL

The relationships between difficulty swallowing and food bolus obstruction with dietary intake, 12-item FAACT A/CS, 5-item anorexia symptoms, and 4-item anorexia concerns are summarized in Table 3. Greater difficulty swallowing and food bolus obstruction were significantly associated with lower dietary intake (according to the Ingesta-VVAS) and worse cachexia-related-QOL (assessed by 12-item FAACT A/CS, 5-item anorexia symptoms, and 4-item anorexia concerns).

Multivariate analysis showed that difficulty swallowing and food bolus obstruction were significantly associated with reduced dietary intake independent of performance status and the presence of cachexia, with coefficients of −0.76 (95% [confidence interval (CI)], −1.48 to −0.054, *P*<0.034) and −1.04 (95% CI, −1.91 to −0.16, *P*<0.019) for difficulty swallowing and food bolus obstruction, respectively (Table 4, 5).

Comment 7:

Discussion: the same comments above and more clear organizations are needed.

Data analysis part can be benefited from including a more clear descriptions after reconsidering the study aims.

Reply 7

Thank you for the comment. We agree and have revised the following text. The newly applied changes are in red font.

(see Page 12, line 276).

[Before revision]

DISCUSSION

To the best of our knowledge, this is the first multicenter study to explore the relationships of throat complications, that is deglutition difficulties and food bolus obstruction, with the ER-QOL and dietary intake in patients with advanced cancer in a palliative care setting. This study demonstrated that throat complications were independently associated with the ER-QOL and dietary intake in patients with advanced cancer in palliative care settings.

We determined the prevalence of and risk factors for throat complications in patients in an advanced palliative care setting, and confirmed that throat complications are associated with reduced dietary intake and lower ER-QOL. Difficulty swallowing and food bolus obstruction were observed in 26.5% and 28.3% of our participants, respectively. The frequency of dysphagia is 5%–54% across all

stages of cancer (2,3,15). However, to the best of our knowledge, no study has assessed the frequency of food bolus obstruction in patients with cancer. In this study, the frequency of food bolus obstruction was significantly higher during and after chemotherapy. Furthermore, previous studies suggested that throat complications were frequently observed not only in patients with head and neck cancers but also in patients with other types of cancer (15). In this study, throat complications were also frequently found in patients with lung (deglutition difficulty, 36%; food bolus obstruction, 38.7%), liver, biliary system, pancreas (deglutition difficulty, 21.1%; food bolus obstruction, 21.1%), and breast (deglutition difficulty, 20.0%; food bolus obstruction, 20.0%) cancers. These results indicate that throat complications are a common symptom of cancer, regardless of the primary site of origin.

This study indicated that patients with advanced cancer, especially older male patients with head and neck cancer and worse ECOG-PS, were likely to have deglutition difficulty and food bolus obstruction, both during and after treatment. This finding is consistent with those of previous studies (15,16,17). Therefore, healthcare providers must consider the possibility of throat complications when providing care to this vulnerable patient population.

Most importantly, the ER-QOL and dietary intake deteriorated with the worsening of deglutition difficulty and food bolus obstruction. Dysphagia was associated with a dysphagia-specific health-related QOL impairment (16). In this study, besides the performance status and cachexia, deglutition difficulty and food bolus obstruction were independently associated with the ER-QOL. Furthermore, deglutition difficulty and food bolus obstruction negatively affected QOL related to cachexia symptoms and concerns. Ingenuity in food form and enhanced rehabilitation should be considered to improve deglutition difficulty and food bolus obstruction in these patients. However, although there is limited availability of treatments in palliative care settings (17), deglutition difficulty and food bolus obstruction need to be diagnosed and treated carefully with fiberoptic endoscopic or videofluoroscopic examination of swallowing to improve ER-QOL, independently of the performance status and cachexia.

The strengths of the present study include the high response rate of participants to the questionnaire, its multicentric design, and the use of validated measurement tools. However, this study had some limitations. First, as the present study is a cross-sectional analysis of a questionnaire survey, the casual relationship of each factor related to throat complications was not confirmed. Second, as data of non-responding patients were not obtained, a comparison between responding and non-responding patients was not possible. Finally, as patients who were forbidden to eat by the primary physician for medical reasons were excluded, the findings of this study might underestimate the proportion and magnitude of deglutition difficulty and food bolus obstruction.

[After revision]

DISCUSSION

To the best of our knowledge, this is the first multicenter study to explore the relationships between swallowing disorders including difficulty swallowing and food bolus obstruction, with cachexia-related QOL and dietary intake in patients with advanced cancer in a palliative care setting. This study

demonstrated that swallowing disorders were independently associated with cachexia-related QOL and dietary intake in patients with advanced cancer in palliative care settings.

We determined the prevalence and risk factors for swallowing disorders in patients in an advanced palliative care setting and confirmed that swallowing disorders are associated with reduced dietary intake and lower cachexia-related QOL. Dysphagia and food bolus obstruction were observed in 26.5% and 28.3% of our participants, respectively. The frequency of difficulty swallowing is 5%–54% across all stages of cancer (11, 27-29). However, to the best of our knowledge, no study has assessed the frequency of food bolus obstruction in patients with cancer. In this study, the frequency of food bolus obstruction was significantly higher during and after chemotherapy. Furthermore, a previous study reported that dysphagia was statistically associated with head and neck cancer (11), while another study suggested that swallowing disorders were frequently observed not only in patients with head and neck cancer but also in patients with other types of cancer (29). In this study, swallowing disorders were also frequently found in patients with cancer of lung (difficulty swallowing, 36%; food bolus obstruction, 38.7%), liver, biliary system, pancreas (difficulty swallowing, 21.1%; food bolus obstruction, 21.1%), and breast (difficulty swallowing, 20.0%; food bolus obstruction, 20.0%). These results indicate that swallowing disorders are a common symptom of cancer, regardless of the primary site of origin. This study also indicated that patients with advanced cancer, particularly older male patients with head and neck cancer and worse ECOG-PS, were likely to have difficulty swallowing and food bolus obstruction, both during and after treatment. This finding is consistent with those of previous studies (29-31). Therefore, healthcare providers must consider the possibility of swallowing disorders when providing care to this vulnerable patient population.

Most importantly, cachexia-related QOL and dietary intake deteriorated with the worsening of difficulty swallowing and food bolus obstruction. Difficulty swallowing was associated with a dysphagia-specific health-related QOL impairment (30). In this study, besides the performance status and cachexia, difficulty swallowing and food bolus obstruction were independently associated with cachexia-related QOL. Furthermore, difficulty swallowing and food bolus obstruction negatively affected QOL related to cachexia symptoms and concerns. Ingenuity in food form and enhanced rehabilitation should be considered to improve difficulty swallowing and food bolus obstruction in these patients. However, although there is limited availability of treatment in palliative care settings (31), difficulty swallowing and food bolus obstruction must be diagnosed and treated carefully with fiberoptic endoscopic or videofluoroscopic examination of swallowing to improve cachexia-related QOL, independent of the performance status and cachexia.

The strengths of the present study include the high response rate of participants to the questionnaire, its multicentric design, and the use of validated measurement tools. However, this study had some limitations. First, as the present study is a cross-sectional analysis of a questionnaire survey, the causal relationship of each factor related to swallowing disorders was not confirmed. Second, as data of non-

responding patients were not obtained, a comparison between responding and non-responding patients was not possible. Finally, as patients who were forbidden to eat by the primary physician for medical reasons were excluded, the findings of this study might underestimate the proportion and magnitude of difficulty swallowing and food bolus obstruction.

Reviewer B

Comment 1:
The background is very poor.

Reply 8

Thank you for bringing this to our notice. We agree and have revised the following text. The newly added changes are in red font.
(see Page 5, line 91).

[Before revision]

INTRODUCTION

The sensation of solid food or liquids moving down the throat is integral to meal enjoyment, and swallowing cold, carbonated water relieves thirst (1). However, cancer progression causes dysphagia in many patients, including those with head and neck cancers (2), and patients with cancer and throat complications presumably experience ageusia (3). Thus, patients with advanced cancer and their families can suffer from eating-related distress. This complex entity encompasses patients' struggle to nourish themselves, emotional and social consequences of the inability to maintain food intake, and profound disturbance in family relationships (4). However, to the best of our knowledge, few studies have investigated the association between throat complications and eating-related quality of life (ER-QOL) in patients with advanced cancer receiving palliative care. This study aimed to explore the potential associations between throat complications – namely, deglutition difficulties and food bolus obstruction – and ER-QOL as well as with the dietary intake in patients with cancer. We present the following article in accordance with the STROBE reporting checklist.

[After revision]

INTRODUCTION

Cancer cachexia is a multifactorial syndrome involving the constant loss of skeletal muscle mass with or without fat mass loss that cannot be completely reversed by usual nutritional care and can lead to progressive functional impairment (1, 2). This occurs due to negative protein and energy imbalances resulting from a combination of reduced dietary intake, hypo-anabolism, and hyper-catabolism in systemic inflammation (1, 2). The prevalence of cachexia ranges from 50–80% in advanced cancer, and

it can be considered the cause of death in 20–30% of cases (3). However, to date, there is no standard strategy for combating cancer cachexia despite its high frequency and negative impact on survival and quality of life (QOL) of patients with cancer (4,5).

In systemic inflammation, pro-inflammatory cytokines act through changes in the central nervous system, particularly the hypothalamic–pituitary–adrenal axis and sympathetic nervous system (6). Thus, exposure to pro-inflammatory cytokines in the central nervous system evokes anorexia and reduced dietary intake in patients with advanced cancer, although increasing dietary intake is a principal component of cancer cachexia management (6). In addition, patients frequently suffer from nutritional impact symptoms, which reduce dietary intake and promote weight loss, including pain, nausea and vomiting, taste and smell disturbances, drowsiness, and depression, leading to impaired physical function and deteriorated QOL (6-10).

An observational study conducted in patients with various types of advanced cancer in palliative care settings demonstrated that oral issues result in nutritional impact symptoms that in turn influence the physical, social, and psychological well-being of patients; therefore, such oral issues must be assessed in the early stages to prevent an inability to eat or drink (11). The study also showed a strong relationship between mucositis, dry mouth, and swallowing disorders (11). Among oral issues, difficulty swallowing and food bolus obstruction directly cause reduced dietary intake; these are commonly observed symptoms that lead to cachexia in patients with advanced cancer (6-9). As some of these patients may benefit from oral care to mitigate nutritional impact symptoms and nutritional care to increase dietary intake, they must be provided with the opportunity to receive optimal care (12, 13).

In previous studies that measured QOL of patients with difficulty swallowing and food bolus obstruction, Swallowing QOL questionnaire (SWAL-QOL) and the Swallowing Quality of Care questionnaire (SWAL-CARE), which measure overall QOL, were the tools used (14-16). According to these studies, lower difficulty swallowing and food bolus obstruction were significantly associated with a better overall QOL. However, to the best of our knowledge, the associations of difficulty swallowing and food bolus obstruction with reduction in dietary intake and impaired QOL remain unknown among patients with advanced cancer in palliative care settings. Therefore, this study aimed to investigate the prevalence and severity of difficulty swallowing and food bolus obstruction and examine the effect of these symptoms on dietary intakes and cachexia-related QOL. We present the following article in accordance with the STROBE reporting checklist.

Comment 2:
Some aspects of the methodology are unclear, which is essential in such an important and sensitive issue as this one. For example, did the people responsible for providing the questionnaires have any training?

Reply 9

Thank you for bringing this to our notice. we have revised the following text. The newly included changes are indicated in red font.

(see Page 6, line 135).

[Before revision]

METHODS

This research comprises a sub-analysis of data from a multicenter self-reported questionnaire-based study that aimed to develop measurement tools for the evaluation of eating-related distress in patients with advanced cancer. The study was conducted at specialist palliative care services (i.e., palliative care outpatient services, hospital palliative care teams, and palliative care units) across 11 hospitals in Japan between July 2020 and July 2021. Consecutive eligible patients were enrolled if they were newly referred for palliative care at the participating institutes during the study period. All institutions were asked to collect information from a designated number of patients that was decided according to the size and location of the institution. The inclusion criteria were: 1) new referral to palliative care; 2) age ≥20 years; 3) diagnosis of locally advanced or metastatic cancer (including hematological neoplasms); 4) awareness of the diagnosis of malignancy; and 5) the ability to respond to a self-reported questionnaire. This analysis excluded patients who: (1) were forbidden to eat by the primary physician for medical reasons and (2) had serious psychological distress that was recognized in an interview with the palliative care physician. Moreover, patients who refused to participate in the study were excluded.

The present study was conducted in accordance with the ethical standards of the Declaration of Helsinki and the ethical guidelines for medical and health research involving human subjects issued by the Ministry of Health, Labor and Welfare in Japan and was approved by the National Cancer Center Research Ethics Review Board (approval number: 2020-070). Japanese law does not require individual informed consent from participants in a non-invasive observational trial such as this study. If patients did not want to participate, we requested they return the questionnaire with “no participation” indicated. The completion and return of the questionnaire were regarded as the consent to participate.

Measurement

Dependent variables

Patients were asked to 1) assess their dietary intake using the ingesta-Verbal/Visual Analogue Scale (ingesta-VVAS) (5) and 2) rate their throat complications, namely, difficulty swallowing and food bolus obstruction, on an 11-point Numeric Rating Scale (NRS) (6); high scores indicated better dietary intake, greater difficulty in swallowing, and worse food bolus obstruction. The ER-QOL of cancer patients was assessed using the Functional Assessment of Anorexia/Cachexia Therapy (FAACT), with a higher score indicating a better QOL. The FAACT is a patient-reported outcome measure that was originally designed to assess specific symptoms and concerns (7,8). The 12 items included in the FAACT Anorexia/Cachexia Subscale (FAACT A/CS) specifically measure cachexia-related symptoms and

concerns, and may be scored separately to yield a domain score (9). In addition, the 5-item anorexia symptom and 4-item anorexia concern subscales that are derived from the 12-item FAACT A/CS are useful for determining anorexia-related symptoms and concerns in patients with lung cancer (10). These subscales have been used to evaluate the effects of treatment on cachexia in patients with advanced cancer (10,11).

Independent variables

Information on patient demographics and clinical characteristics, including sex, age, primary cancer site, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (12), and treatment status (pre-chemotherapy, chemotherapy, and never treated/previously treated), were obtained through self-reported questionnaires. Anthropometric measurements, such as height, current body weight, and previous body weight, were self-reported by the patients and were used to calculate body mass index (BMI) and percent weight loss (%WL) over 6 months. BMI was calculated by dividing the current body weight (kg) by the height in meters squared (m^2); %WL was calculated as follows: %WL= (current body weight [kg] − previous body weight [kg]) / previous body weight (kg) × 100.

Statistical analysis

The primary endpoints were throat complications, namely, deglutition difficulties and food bolus obstruction, ER-QOL, and dietary intake. Patients with missing data related to the primary endpoints were excluded from the analysis. Patient demographics and clinical characteristics are presented as the number and percentage (%) for categorical variables and as mean with standard deviation (SD) for continuous variables, as appropriate. Cachexia was diagnosed based on the criteria from the international consensus: %WL in 6 months ≥5% or BMI <20 kg/m^2 + %WL in 6 months ≥2%. Patients with scores above or below these cutoff values were classified into a non-cachexia group or cachexia group, respectively (13).

To examine the impact of deglutition difficulty (NRS≥1) and food bolus obstruction (NRS≥1), we used independent-sample *t*-tests and analysis of variance (ANOVA) to identify variables that were considered potential confounders, including sex, age, primary cancer site, ECOG-PS, treatment status (pre-chemotherapy, chemotherapy, and never treated/previously treated), and cachexia (non-cachexia vs. cachexia). We classified throat complications (deglutition difficulty and food bolus obstruction) into three groups based on NRS scores of 0, 1–3, and ≥4. To investigate the relationships between deglutition difficulty, food bolus obstruction, and dietary intake, we performed independent-sample *t*-tests and ANOVA to compare the 12-item FAACT A/CS, 5-item anorexia symptoms, and 4-item anorexia concerns among the three patient subgroups.

To assess the effects of deglutition difficulty and food bolus obstruction on the 12-item FAACT A/CS score and dietary intake, a crude estimation was performed using a robust linear model. The multivariate model was adjusted for sex, age (two age groups: <69 and ≥70 years), primary cancer site, ECOG-PS (two groups: PS 0–2 and PS 3–4), treatment status (pre-chemotherapy, chemotherapy, and never treated/previously treated), and cachexia (non-cachexia vs. cachexia). All results with a *P*-value

<0.05 were considered significant. All statistical analyses were performed using SPSS (version 28.0.1, IBM Corp., Armonk, NY, USA, USA) and EZR (Saitama Medical Center, Jichi Medical University) (14).

[After revision]

METHODS

This study comprises a sub-analysis of data obtained from a multicenter self-reported questionnaire-based study that aimed to develop measurement tools for the evaluation of eating-related distress in patients with advanced cancer. The methodology applied in that study has been described and published previously (17). In brief, the study was conducted at specialist palliative care services (i.e., palliative care outpatient services, hospital palliative care teams, and palliative care units) across 11 hospitals in Japan between July 2020 and July 2021. Consecutive eligible patients were enrolled if they were newly referred for palliative care at the participating institutes during the study period. All institutions were asked to collect information from a designated number of patients that was decided according to the size and location of the institution. The inclusion criteria were: 1) new referral to palliative care; 2) age ≥20 years; 3) diagnosis of locally advanced or metastatic cancer (including hematological neoplasms); 4) awareness of the diagnosis of malignancy; and 5) the ability to respond to a self-reported questionnaire. This analysis excluded patients who: (1) were forbidden to eat by the primary physician for medical reasons and (2) had serious psychological distress that was recognized in an interview with the palliative care physician. Moreover, patients who refused to participate in the study were excluded.

The present study was conducted in accordance with the ethical standards of the Declaration of Helsinki and the ethical guidelines for medical and health research involving human subjects issued by the Ministry of Health, Labor and Welfare in Japan and was approved by the National Cancer Center Research Ethics Review Board (approval number: 2020-070). Japanese law does not require individual informed consent from participants in a non-invasive observational trial such as this study. If patients did not want to participate, we requested they return the questionnaire with “no participation” indicated. The completion and return of the questionnaire were regarded as consent to participate.

Measurement

Demographic and clinical characteristics

Demographics and clinical characteristics, including sex, age, primary cancer site, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (18), and treatment status (pre-chemotherapy, chemotherapy, and never treated/previously treated), were obtained from self-reported questionnaires. Anthropometric measurements, such as height, current body weight, and previous body weight, were self-reported by the patients and were used to calculate body mass index (BMI) and percent weight loss (%WL) over 6 months. BMI was calculated by dividing the current body weight (kg) by the height in meters squared (m^2); %WL was calculated as follows: %WL = (current body weight [kg] − previous body weight [kg]) / previous body weight (kg) × 100.

Difficulty swallowing and food bolus obstruction

Patients were asked to assess current difficulty swallowing and food bolus obstruction using an 11-point Numerical Rating Scale (NRS) (9, 10, 19), where 0=no difficulty swallowing and food bolus obstruction and 10=worst possible difficulty swallowing and food bolus obstruction; higher scores indicated more severe disturbances.

Dietary intake and cachexia-related QOL

Patients were asked to assess their dietary intake using the Ingesta–Verbal/Visual Analog Scale (Ingesta-VVAS) (20). Higher Ingesta-VVAS scores indicated better dietary intake. Cachexia-related QOL was assessed using the Functional Assessment of Anorexia/Cachexia Therapy Anorexia Cachexia Subscale (FAACT ACS), with higher scores indicating better QOL. The FAACT ACS is a patient-reported outcome measure originally designed to assess specific symptoms and concerns. The 12 items of the FAACT ACS specifically measure cachexia-related symptoms and concerns that may be scored to yield a domain score. In addition, subscales derived from the 12-item FAACT ACS, which included the five-item anorexia symptoms and four-item anorexia concerns were demonstrated to be useful for assessing these parameters in patients with lung cancer. These subscales have also been applied to evaluate the treatment effects of cachexia in patients with advanced cancer (21-24). The Japanese version of the FAACT ACS has been published by the developers (25).

Statistical analysis

The primary endpoints were difficulty swallowing, food bolus obstruction, dietary intake, and the FAACT ACS. We excluded patients with missing data related to the primary endpoint from the analysis. Patient demographics and clinical characteristics are presented as number (%) for categorical variables and mean (standard deviation [SD]) for continuous variables, where appropriate. Cachexia was defined as a %WL over the previous 6 months ≥5% or BMI <20 kg/m^2 + %WL over the previous 6 months ≥2%, based on international consensus criteria (1).

To examine the impact of difficulty swallowing (NRS ≥1) and food bolus obstruction (NRS ≥1), we used independent-sample t-tests and analysis of variance (ANOVAs) to explore potential confounding variables such as sex, age, primary cancer site, ECOG PS, anticancer treatment status (pre-chemotherapy, chemotherapy, and never treated/previously treated), and cachexia (non-cachexia and cachexia).

We classified difficulty swallowing and food bolus obstruction into three levels for analysis based on previous research: NRS=0 was defined as none, NRS=1–3 as mild, and NRS ≥4 as moderate to severe (10). Independent-samples t-tests and ANOVAs were used to investigate the relationships among difficulty swallowing (three groups), food bolus obstruction (three groups), dietary intake, FAACT ACS 12-item, 5-item anorexia symptoms scores, and 4-item anorexia concerns scores (24).

To assess the effects of dietary intake and FAACT ACS 12-item on difficulty swallowing and food bolus obstruction, we developed a robust linear model with crude estimation. Variables with significant differences were included in the multiple logistic regression model as independent variables. The multiple logistic regression model was used to identify factors associated with levels of difficulty swallowing and food bolus obstruction. The dependent variable was difficulty swallowing and food bolus obstruction status, which was classified into categories of “none,” “mild,” and “moderate to severe” levels of difficulty swallowing and food bolus obstruction. A multivariate model adjusted for sex, age (two groups: <69 years and ≥70 years), primary cancer site, ECOG PS (two groups: PS: 0–2 and PS: 3–4), treatment status (pre-chemotherapy, chemotherapy, and never treated/previously treated), and cachexia (non-cachexia and cachexia) was generated. Significance was set at $P < 0.05$. All analyses were performed using SPSS version 28.0.1 (IBM Corp., Armonk, NY, USA) and EZR (Saitama Medical Center, Jichi Medical University) (26).

Comment 3:
What is lacking in this type of topic is a mixed investigation, where the patient is questioned in a calm manner. A qualitative part of the research would have been desirable.

Reply 10
We agree with the above comment; however, since this study was a secondary analysis, qualitative evaluation was difficult. We would like to consider this in our next study.

Comment 4:
“healthcare providers need to pay attention to any throat symptoms in patients with cancer, including head and neck cancers, irrespective of the primary site of origin". This is not a particularly relevant contribution to the scientific community.

Reply 11
Thank you for bringing this to our notice. we have revised the following text in red font.
(see Page 14, line 331).

[Before revision]
Therefore, healthcare providers need to pay attention to any throat symptoms in patients with cancer, including head and neck cancers, irrespective of the primary site of origin.

[After revision]

Thus, healthcare providers must diagnose and treat swallowing disorders, such as difficulty swallowing and food bolus obstruction, in a timely manner to prevent progression of cachexia and improve cachexia-related QOL.