Cancer Cachexia and Dysphagia: A Systematic Literature Review

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Abstract

BACKGROUND: Dysphagia is a difficulty in swallowing. Cancer cachexia is a generalised muscle loss disorder common in patients with late-stage disease. The prevalence of dysphagia in patients with head and neck cancer is well documented. However, it is postulated that cancer cachexia can, through systemic muscle loss, cause weakening of swallowing muscles and dysphagia. This review aimed to evaluate the scope of the association between cancer cachexia (excluding head and neck cancer) and dysphagia.

METHODS: A systematic review was conducted using the PRISMA P guidelines. PubMed and Embase databases were searched for papers including terms related to (1) cancer, (2) cachexia and (3) dysphagia. Results were imported to Zotero software manager, where duplicates were removed. The remaining articles were screened using pre-determined eligibility criteria. Eligible papers were retained for data extraction, data synthesis and narrative synthesis. Risk of bias was evaluated using the CASP cohort and case control tools.

RESULTS: Four studies met the eligibility criteria. These papers reported an association between cancer cachexia and dysphagia, with odds ratios of 2.1 [P=0.033] and 1.8 [P=0.018]. Prevalence of dysphagia was 16% higher in cancer patients with cachexia.

CONCLUSION: These findings suggest a positive association between cancer cachexia and dysphagia. However, due to the limited number of papers included, their heterogeneity and their limitations, it is difficult to draw a robust conclusion. Sarcopenia or neurodegenerative disease may have contributed to these results. Regardless, these four studies support the requirement for dysphagia assessment in patients with cancers outside swallow regions.

Background

Dysphagia, defined by the Royal College of Speech and Language Therapists (RCLST), pertains to eating and drinking disorders that can affect the oral, pharyngeal, and oesophageal stages of deglutition [1]. It involves the intricate interplay of respiratory, oral, pharyngeal, laryngeal, and oesophageal structures working in harmony to propel a bolus to the stomach. Muscular and sensory innervation of these structures is vital. Swallowing impairment is often due to structural changes, inflammation at any point along the bolus pathway, neurological issues, or muscular deficits. Diagnosis involves a combination of assessments, including a detailed case history, cranial nerve evaluation through an oral-motor examination, bedside food and fluids trials, and objective swallowing assessments such as videofluoroscopic swallowing studies (VFSS), fibre-optic endoscopic evaluation of swallowing (FEES), and high-resolution pharyngeal manometry [2].

Dysphagia can occur in the oropharyngeal and oesophageal stages. Oropharyngeal dysphagia results from dysfunction in structures like the lips, teeth, tongue, epiglottis, hard and soft palates. It is often associated with head and neck cancers and their radiotherapy [3]. Esophageal dysphagia, on the other hand, relates to the inability to propel the bolus from the oropharynx to the stomach. It may be caused by obstructions (e.g., stricture or tumour) or functional (mechanical) disorders like nerve damage, esophagitis, or achalasia.

Dysphagia is a common complication in cancer patients [4] and a complex condition influenced by several cancer-associated factors. Head and neck

https://doi.org/10.33178.SMJ.2024.1.4

tumours have a direct impact on swallowing, with dysphagia present in 89% of patients with head and neck cancer [5]. It can be attributed to tissue loss, structural damage, or obstruction due to the tumour mass. Tumours in the brain or brainstem can disrupt neural connections, affecting swallowing [6]. Aspiration pneumonia is a frequent consequence of dysphagia [7] and contributes to the mortality of head and neck cancer patients [8]. The association between head and neck cancer and dysphagia is well-documented, but dysphagia in cancers outside the swallowing regions is underexplored [5].

Cancer treatment, including tumour resection, radiotherapy, and chemotherapy, can impact dysphagia. Head and neck surgery may leave tissue scarring, reducing muscle function and potentially impairing swallowing coordination if nerves are damaged. Radiotherapy's impact on dysphagia depends on the irradiation site. It damages DNA in rapidly proliferating cells, leading to tumour cell destruction but may also harm healthy tissue organelles, causing transient cell damage and leading to acute dysphagia. Additionally, radiation may induce chronic dysphagia through tissue fibrosis, reducing muscle function and causing atrophy [9]. This study focuses on the aspect of dysphagia related to muscle mass loss.

Cachexia is a complex weight loss disorder caused by illness. The condition is characterised by severe and unintentional loss of muscle (and fat mass in some cases) which cannot be fully reversed by nutrition. Cachexia affects 50-80% of cancer patients [10], particularly in late-stage cancer. Cancer cachexia requires a meticulous multimodal clinical examination for diagnosis. The condition is defined as “weight loss greater than 5%, or weight loss greater than 2% in individuals already showing depletion” [11].

Muscle wasting in cancer cachexia primarily involves inflammation. Tumours boost the production of inflammatory mediators and tumour-derived compounds, like proteolysis-inducing factor (PIF), which breaks down myofibrillar proteins. PIF and cytokines activate nuclear factor-kB, leading to skeletal muscle atrophy, as well as janus kinase MAPK cascades, resulting in apoptosis and cell death [12].

Cachexia affects metabolic pathways as tumours demand significant glucose and amino acids for their proliferation. Skeletal muscle proteins are often broken down to produce glutamine for tumour protein synthesis and alanine for glucose production in the liver. To maintain homeostasis in the presence of a tumour, substantial metabolic changes occur, causing systemic skeletal muscle loss [13]. This cachectic muscle loss is not confined to the tumour's immediate vicinity, reflecting the systemic characteristic of cancer-mediated inflammation.

Cancer cachexia is associated with poor prognosis [14]. Patients achieve low scores in quality-of-life surveys and the Karnofsky Performance Scale, and regularly present with decreased food intake, fatigue and reduced range of motion [15]. Cancer cachexia accounts for 20% of cancer deaths, which typically ensues as weight loss surpasses 30-40% [16]. There is a clear association between cachectic muscle loss and reduced food intake. There is also an association between generalised muscle loss and dysphagia. However, systemic muscle loss due to cachexia is not well investigated as a factor which contributes to dysphagia.

Dysphagia in patients with unrelated cancer is frequently overlooked, which could result in poorer patient quality of life, impaired nutrition or aspiration pneumonia in later-stage patients. Dysphagia could, through a cachectic muscle loss mechanism, arise in patients with cancers unrelated to swallow function [17] . However, few studies have identified cachexia as a causal factor for dysphagia. This systematic review of the literature aims to evaluate the scope of the association between cancer cachexia (excluding head and neck cancer) and dysphagia.

Methods

SOURCE

The databases used for this review were PubMed and Embase. These were selected for their advanced searching functions and facilitation of the use of Medical Subject Heading (MeSH) terms. PubMed was chosen over MEDLINE as PubMed contains additional content outside the scope of the MEDLINE database. Additional related papers were also assessed through referencing lists (PubMed’s “Related citations” feature and Embase’s “Find Similar” features); however none were deemed eligible for this review. Database searching was the only source of data included in this review.

SEARCH STRATEGY

Preliminary searches were performed in January 2022, however minor adjustments were made to the search terms. The terms "tumour" and "tumours" were added to increase the number of papers identified. The final search was performed on 25 February 2022. Identical terms were used in each database. Neither search utilized a timeframe. The search terms used for PubMed were (cancer[Title] OR cancers[Title] OR tumour[Title] OR tumours[Title] OR tumour[Title] OR tumours[Title] OR malignancy[Title] OR malignancies[Title] OR carcinoma[Title] OR carcinomas[Title]) AND (cachexia OR sarcopenia OR malnutrition OR atrophy OR "muscle wastage" OR "muscle wasting") AND (dysphagia OR 'eating-related stress' OR 'difficulty swallowing' OR "trouble swallowing" OR "swallowing disorder" OR "swallowing disorders" OR "deglutition disorder").

"Cancer" and related terminology referred to the patient population of interest. The MESH terms related to cancer were specified to have been included in the title to ensure that populations were cancer-specific and not related to another disease. The Embase search included ":ti" after each cancer-related term, to ensure that those terms must be included in the title, mirroring the PubMed search. No other restrictions were used to maximise the scope of the search.

The exposure was "cachexia" and other muscle loss-related terms. This search encompassed anorexia cachexia syndrome. "Sarcopenia" was added to include papers which may have grouped together these nutrition-based disorders, as seen during early database searches.

The outcome was searched using "dysphagia" and a few other terms related to deficits in swallowing. Prior to protocol completion, preliminary searches identified "difficulty swallowing" and other such terms as being used interchangeably. While the absence of the term "dysphagia" may be indicative of the use of a weak definition, "swallowing" terminology was included to capture a wider array of papers.

INCLUSION CRITERIA

Studies included in the review were required to include full free-text links and to have been written in English. All years were included. Only observational studies were assessed, including cohort, case-control, cross-sectional and case series studies. Patient demographics must have been over the age of 18. Patients with primary tumours outside the head, neck, and upper gastrointestinal tract were included. Papers which included these cancers but accounted for primary cancer site as a covariate in the statistical analysis were also included.

EXCLUSION CRITERIA

Interventional studies, such as randomised controlled trials, were all excluded. This review focused purely on the association between cancer cachexia and dysphagia. Therefore, studies focusing on treatment efficacy would not provide useful results. Research papers without free access or access through Embase or PubMed subscription were excluded. The review was patient-focused, excluding animal and preclinical models.

Regarding cancer types, a number were excluded due to their potential to impact dysphagia through a non-cachectic mechanism. Papers with a sole focus on cancers of the head and neck, and upper gastrointestinal tract were excluded, as these are seen to impact dysphagia directly. Gastric cancers have been linked to dysphagia and were also excluded (Maconi et al., 2008). The review also excluded patients with neurodegenerative diseases. Patients who had undergone radiotherapy or surgery interventions to the chest, head or neck regions were also excluded.

STUDY SELECTION

Results of the database searches were imported to Zotero Software Manager. This program facilitated the storage of citations and was also used to merge duplicate papers. Merging was performed manually with the most recent version of a text retained. The data of the remaining citations were imported into Microsoft Excel for the initial screening. Texts were evaluated based on title and abstract and were removed based on inclusion and exclusion criteria. Remaining papers were sought for retrieval. Those with accessible free full-text articles were thoroughly evaluated for eligibility criteria. Four papers fit these criteria and were retained for the final review. The Prisma 2009 Flow Diagram was used to record the number of papers at each stage of the screening process.

DATA EXTRACTION

Data were extracted using a specialised data

extraction form in line with the PICO framework that was designed to fit the research (see Appendix 1). Information was extracted under seven headings. Bibliographical information included the title, author, and funding source. The objectives column captured the aims of each paper. The study design and methodology column included data on study type, population type, recruitment methods, sample size, eligibility criteria and a brief overview of the study. In the exposure column, patient characteristics and cachexia definition were recorded. Outcomes included the definition of dysphagia. The results column recorded the association between cancer cachexia and dysphagia noted in each paper, as well as any relevant notes or conclusions in the paper relevant to these associations. A strengths and limitations column was also added to assist in gathering data that would help evaluate these papers.

QUALITY ASSESSMENT

Risk of bias and overall study quality was evaluated using the CASP Cohort and Case-Control checklists. Of the four selected papers, two were cross-sectional studies, one was a case-control study, and one was a post hoc analysis of prospective cohort data. CASP tools were chosen over other tools as use of the same type of tool facilitated a more thorough comparison. The use of the cohort tool for cross-sectional studies meant that questions 6. (a) and 6. (b), relating to follow-up (Table 4) were non-applicable and were excluded. Using the Web of Science database, the number of citations of each paper was recorded.

SYNTHESIS OF RESULTS

A narrative approach was taken to data synthesis. Different statistical approaches were taken by each paper, and the use of meta-analysis with both odds ratios and prevalence values may have generated unreliable results. There was significant heterogeneity between exposure measurements and outcome definitions used in each paper and therefore a comparison between their findings was made in the context of these definitions and not in a quantitative manner. Relevant findings of the four selected papers were synthesized in three tables, examining study characteristics, participant characteristics and results.

Results

SEARCH RESULTS

712 papers were screened by title and abstract, resulting in the retrieval and evaluation of 59 texts based on eligibility criteria. Four studies met these criteria and underwent quality appraisal and data extraction. The PRISMA diagram (Fig. 1) displayed exclusion criteria for eliminating full-text articles. Results of each paper were synthesized in Table 1, 2, and 3.

DESCRIPTION OF STUDIES

Out of the four selected studies, two were cross-sectional [18,19], one was a case-control [20], and one was a post hoc analysis of prospective cohort data [21]. These studies were conducted in developed countries, with two in Japan [19,20], one in Ireland [18], and one in the US [21]. Their objectives varied, with two studies aimed at identifying factors contributing to eating-related distress and dysphagia [18,19], one focused on generating a symptom profile for cancer anorexia cachexia syndrome [21], and one examined the association between skeletal muscle and dysphagia [20]. Kenny et al., 2019, and Lasheen and Walsh., 2010 had relatively large sample sizes of 385 and 484, respectively. Amano et al., 2018, and Wakabayashi et al., 2015 had comparatively smaller sample sizes of 140 and 111, respectively, while still generating similar p-values when compared to the larger studies.

DEMOGRAPHIC CHARACTERISTICS

Differences among participants in each paper included variations in mean patient age: 66, 66, 65, and 70 [18,19,21,20]. The primary tumour site differed, with lung being most common in Amano et al., 2018 (22.1%) and Lasheen and Walsh., 2010 (23%), while Kenny et al., 2019 (15.3%) and Wakabayashi et al., 2015 (11.7%) had lung tumours as the second most common. Colorectal (21.3%) and oesophageal (49.5%) cancer predominated in these papers. Kenny et al., 2019 was the sole study excluding head and neck cancers.

Two studies had all participants with metastatic cancer [19,21]. Kenny et al., 2019 (67%) and Wakabayashi et al., 2015 (26%) displayed significant differences in the proportion of participants at the metastatic stage.

Regarding treatment, limited data was available in Lasheen and Walsh., 2010, stating that "few patients were receiving active treatment." In Kenny et al., 2019, all patients were under treatment, mainly chemotherapy (74%). Amano et al., 2018 saw 63.6% of patients receiving chemotherapy. Information on

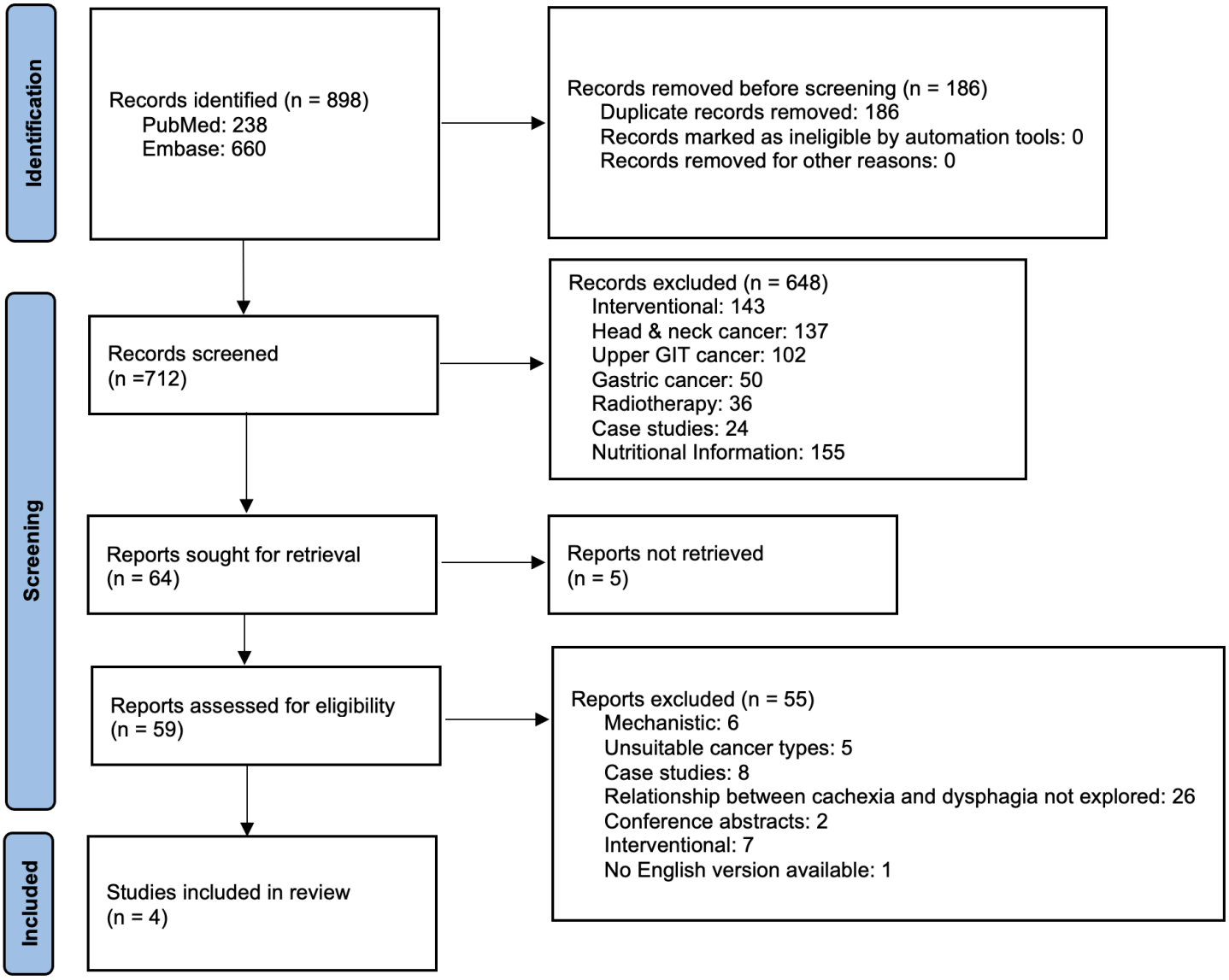

Figure 1: Prisma Diagram

the number of patients receiving radiotherapy was not provided in three studies [19,21,20], and one study reported patients who had undergone surgery [20].

EXPOSURE CHARACTERISTICS

Differences were observed in cachexia measurements and definitions among these papers. Three papers [18,19,21] relied partially on self-reported height and weight data, with two of them [18,21] supplementing this with validated medical records. In contrast, the fourth study [20] used abdominal CT scans to assess skeletal muscle mass instead of BMI. While two papers [18,19] adhered to the international consensus diagnostic criteria for cachexia, which include a 5% body weight loss in 6 months or a BMI under 20 kg/m^2 with a 2% weight loss in 6 months, Lasheen and Walsh., 2010 defined cachexia as a loss exceeding 10% of pre-illness body weight. Wakabayashi et al., 2015 did not employ a validated cachexia definition and measured skeletal muscle index using the psoas muscle area divided by height squared.

OUTCOME CHARACTERISTICS

Variability was evident in the measurement tools and definitions of dysphagia. Three studies [18,19,21] employed patient questionnaires, with one adding a cranial nerve examination [18]. The fourth study20 utilized a 10-point observer-rating scale. Of these, two measurement tools were validated [18,20], while two were unvalidated [19,21].

RESULTS

Despite methodological heterogeneity among these papers, the association between cachexia and

Table 1: Study Characteristics

Author & Year	Title	Country	Sample Size	Population & Setting	Study Design	Aims & Objectives
(Kenny et al., 2019)	Dysphagia Prevalence and Predictors in Cancers Outside the Head, Neck, and Upper Gastrointestinal Tract	Ireland	N=385	Patients with cancer outside the head, neck, or upper GI tract attending two acute hospitals and one hospice.	Cross-sectional	[1] To address gaps in dysphagia identification and management. [2] To profile those most at risk of swallowing difficulties by examining clinical and demographic factors that may influence dysphagia presence.
(Amano et al., 2018)	Eating-related distress in advanced cancer patients with cachexia and family members: a survey in palliative and supportive care settings	Japan	N=140	Palliative care patients in Osaka City General Hospital (all advanced cancer patients).	Cross-sectional	[1] To examine the severity of nutrition impact symptoms in advanced cancer patients and the prevalence of eating-related distress among patients and their family members in palliative and supportive care settings, including outpatient services, palliative and supportive care teams, and the palliative care unit. [2] To compare these parameters between the following groups: (1) non-cachexia/pre-cachexia and (2) cachexia/refractory cachexia.
(Lasheen and Walsh., 2010)	The cancer anorexia-cachexia syndrome: myth or reality?	USA	N=484	One thousand consecutive cancer in- and out-patient consults to the palliative medicine team.	Post hoc analysis of prospective cohort data	[1] To identify the clinical symptom characteristics of CACS. [2] To evaluate CACS independent impact on patient outcomes, assessed by symptom burden, and survival from the time of referral.
(Wakabayashi et al., 2015)	Skeletal muscle mass is associated with severe dysphagia in cancer patients	Japan	N=111	Cancer patients with dysphagia admitted to the Yokohama City University Medical Center and referred to the department of rehabilitation medicine between May 2010 and April 2014.	Case-control	[1] To investigate the association between skeletal muscle mass assessed by abdominal CT, ADLs and severe dysphagia in cancer patients.

Table 2: Demographic Characteristics

Author & Year	Mean Age (Years)	Primary Cancer Site, (%)	Disease Extent, n (%)	Treatment Status, n (%)
(Kenny et al., 2019)	66 (±12)	Bladder (10.1), Brain (0.2), Breast (7.0), Cervix (0.2), Cholangiocarcinoma (0.8), Colorectal (21.3), Gallbladder (0.1), Kidney (10.9), Liver (1.0), Lung (15.3), Mediastinum (0.2), Melanoma (2.1), Mesothelioma (0.8), Ovary (5.2), Pancreas (5.7), Peritoneal: (0.2), Prostate (13.8), Sarcoma (0.1), Testicle (1.3), Thymus (0.2), Uterus (1.3)	Metastatic 257 (67) Locoregional 128 (33)	Medical oncology 286 (74) Palliative care 91 (24) Radiation oncology 8 (2)
(Amano et al., 2018)	66.3 (±11.1)	Lungs (22.1), Upper and lower gastrointestinal tract (22.1), Liver, biliary system, pancreas (12.9), Haematological malignancy (11.4), Urinary system, prostate (10.0), Head and neck (6.4), Breast (5.7), Gynaecology (3.6), Others (5.7)	Metastatic 140 (100)	Pre-chemotherapy 8 (5.7) Chemotherapy 89 (63.6) Never treated/previous treatment 43 (30.7)
(Lasheen and Walsh., 2010)	65 (21-94)	Lung (23), Colorectal (10), Breast (10), Prostate (18), Pelvic (7)	Metastatic 484 (100)	"Few patients were receiving active treatment"
(Wakabayashi et al., 2015)	70 (±10)	Oesophageal (49.5), Lung (11.7), Gastric (9.9), Brain (5.4), Colon (4.5), Prostate (4.5), Hepatocellular (1.8), Thyroid (1.8), Pharyngeal (1.8), Others (9.0)	Stage I 20 (19) Stage II 19 (18) Stage III 39 (37) Stage IV 27 (26)	Surgery 71 (64) Without surgery 40 (36)

dysphagia remained relatively consistent. While Kenny et al., 2019 and Wakabayashi et al., 2015 examined different factors (cachexia versus skeletal muscle index) and outcomes (dysphagia versus oral food intake), both studies indicated a significant link between muscle loss and swallowing difficulties (2.1 (1.1-4.0) and 1.8 (1.1-3.0), respectively). Cachectic patients had a dysphagia prevalence of 28%, compared to 12% in non-weight loss patients [21]. Amano et al., 2018 also demonstrated increased dysphagia prevalence in cachexia-affected patients (2(0-5)) compared to non-cachectic patients (0(0-2)). All four papers reported similar p-values, indicating statistical significance: $P=0.033$ [18], $P=0.002$ [19], $P<0.05$ [21], and $P=0.018$ [20].

Regarding control of covariates, three studies considered primary cancer site, one excluding relevant tumours in the study design18, while the others employed logistic regression20,21. Age, gender, and Eastern Cooperative Oncology Group (ECOG) were the common covariates in three of the studies [18,20,21], though Amano et al., 2018 did not adjust for any covariates.

QUALITY OF STUDIES

CASP checklists were employed to assess the quality of these papers, revealing a range of risk or bias, from low to moderate. Three studies were classified as having low bias risk, as they diligently identified and addressed confounding factors to prevent them from impacting the results [18,20,21]. However, Amano et al., 2018 failed to identify head and neck cancer as a potential confounder and did not use statistical methods to account for other influencing factors, which raises concerns about the validity of their results, leading to a moderate risk of bias.

Two studies relied on self-reported height and weight data, introducing a slight chance of bias [18,19]. Additionally, two papers used diagnostic tools not specific to dysphagia, and the validity of these tools remains uncertain [19,21]. Only Kenny et al., 2019 provided precise results, indicated by narrow confidence intervals and low p-values. The precision of the other three studies was unclear due to wide confidence intervals [19], unreported confidence intervals [21], and $P<0.05$ reported in only a small number of variables [20].

Three of the studies are applicable to a local population, as they employed validated international definitions and measurement methods that are feasible for replication [18,19,20]. In contrast, Lasheen and Walsh., 2010 provided limited information regarding their dysphagia diagnosis tool, making it unclear whether it's validated or accessible to other populations.

Discussion

This systematic review explored the link between cancer cachexia (excluding head and neck cancer) and dysphagia. The review revealed a higher dysphagia prevalence in cachexic patients, with a consistent, statistically supported association. However, the limited number of included studies and their divergent methodologies, coupled with a moderate bias risk in one study, challenge the ability to establish a definitive conclusion regarding the relationship between cancer cachexia and dysphagia.

The link between skeletal muscle loss and dysphagia is evident in all these papers. Two studies address the relationship between overall muscle loss and dysphagia [18,20], while the other two studies briefly mention the associations. The exact cause of dysphagia in patients with non-head and neck cancer sites remains uncertain [18]. Reduced food intake is a component of cancer anorexia cachexia syndrome [21], and it's reasonable to assume that this reduced intake might be linked to dysphagia. This dysphagia could be influenced by the cachexia aspect of the syndrome. A study on tongue and arm muscle thickness found that muscle loss can occur both in swallowing areas and generally [22], supporting the use of skeletal muscle indices to indicate muscle changes in swallowing regions. A cachexia-related mechanism could explain the systemic nature of this muscle loss.

The reviewed literature had several limitations. Notably, the studies in this review did not consider conditions like stroke, Parkinson's Disease, or dementia, which contribute to 75% of dysphagia cases in elderly patients [23]. Additionally, there is a risk of bias in some papers, particularly Amano et al., 2018, which failed to account for cancer type, potentially affecting the independence of cachexia-related dysphagia from tumour location. While the Food Intake LEVEL Scale and Functional Oral Intake Scale used in two studies were validated [24,25], the dysphagia assessment measures in the other studies lacked validation. Furthermore, the lack of consensus on cachexia definitions impacts

Table 3: Results

Author & Year	Cachexia Measurement Methods	Cachexia Definition	Dysphagia Measurement Methods	Dysphagia Definition	Results	Covariates Accounted For	Risk of Bias
(Kenny et al., 2019)	Height & weight obtained by medical notes or self-reported.	Body weight loss rate in 6 months ≥ 5% or body mass index < 20 kg/m(2) + in 6 months ≥ 2%. *(Fearon et al., 2011)*	Questionnaire, Cranial Nerve Examination	1. Concrete swallowing difficulties reported during case history, even if these were not observed during swallow trials 2. MASA score #177, MASA aspiration or dysphagia risk anything other than ''unlikely'' 3. FOIS score <7 4. Participant needed to use compensatory strategy *(Mann, 2002)* *(Crary et al., 2005)*	**2.1 (1.1-4.0)** *[P=0.033]* *Cachexia as a predictor of dysphagia*	Anorexia Cough Dysphonia Nausea Wheeze ECOG-PS Taste changes Setting (hospice or hospital) Dyspnoea Cognition Quality of life % Weight loss Health care team Patient location Health care provider HNO radiotherapy Early satiety	Low
(Amano et al., 2018)	Height & weight obtained by self-reported questionnaire.	Body weight loss rate in 6 months ≥ 5% or body mass index < 20 kg/m(2) + in 6 months ≥ 2%. *(Fearon et al., 2011)*	Questionnaire	Patient-Generated Subjective Global Assessment (PG-SGA) *(Bauer et al., 2002)*	**0 (0-2)** *[P=0.002]* *Non-cachexia patients presenting with dysphagia* **2 (0-5)** *[P=0.002]* *Cachexia/refractory patients presenting with dysphagia*	N/a	Moderate
(Lasheen and Walsh., 2010)	Height & weight obtained by medical notes or self-reported questionnaire.	Weight loss >10% of pre-illness body weight *(Blackburn et al., 1977)*	Questionnaire	Empirically derived clinical assessment based on conventional medical history taking. *(Walsh et al., 2000)*	**Prevalence of 28%** *[P<0.05]* *Dysphagia in patients with cachexia* **Prevalence of 12%** *[P<0.05]* *Dysphagia in patients with no weight loss*	Primary cancer site Gender ECOG Age	Low
(Wakabayashi et al., 2015)	C-reactive protein Skeletal muscle mass assessed by abdominal CT.	Skeletal Muscle Index (psoas area/height^2)	10-point observer-rating scale	Food Intake LEVEL Scale *(Kunieda et al., 2013)*	**1.8 (1.1-3.0)** *[P=0.018]* *Skeletal muscle index as a predictor of oral food intake*	Age Sex Albumin Barthel index Cancer stage Cancer type Vocal cord paralysis	Low

Table 4: Quality Appraisal – CASP Cohort Tool

	(Kenny et al., 2019)	(Amano et al., 2018)	(Lasheen and Walsh., 2010)
1. Did the study address a clearly focused issue?	Yes	Yes	Yes
2. Was the cohort recruited in an acceptable way?	Yes	Yes	Yes
3. Was the exposure accurately measured to minimise bias?	Can't tell	Can't tell	Yes
4. Was the outcome accurately measured to minimise bias?	Yes	Can't tell	Can't tell
5. (a) Have the authors identified all important confounding factors?	Yes	No	Yes
5. (b) Have they taken account of the confounding factors in the design and/or analysis?	Yes	No	Yes
6. (a) Was the follow up of subjects complete enough?	n/a	n/a	n/a
6. (b) Was the follow up of subjects long enough?	n/a	n/a	n/a
8. How precise are the results?	Precise *(Narrow CIs / Low p values)*	Can't tell *(Wide CIs / Low p values)*	Can't tell *(No CIs given)*
9. Do you believe the results?	Yes	Can't tell	Yes
10. Can the results be applied to the local population?	Yes	Yes	Can't tell
11. Do the results of this study fit with other available evidence?	Yes	Yes	Yes
12. Does the study have implications for practice?	Yes	Yes	Yes

Table 5: Quality Appraisal – CASP Case Control Checklist

	(Wakabayashi et al., 2015)
1. Did the study address a clearly focused issue?	Yes
2. Did the authors use an appropriate method to answer their question?	Yes
3. Were the cases recruited in an acceptable way?	Yes
4. Were the controls selected in an acceptable way?	Yes
5. Was the exposure accurately measured to minimise bias?	Yes
6. (b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Yes
7. How large was the treatment effect?	Moderate
8. How precise was the estimate of the treatment effect?	Can't tell
9. Do you believe the results?	Yes
10. Can the results be applied to the local population?	Yes
11. Do the results of this study fit with other available evidence?	Yes

the overall strength of the conclusions. Nevertheless, it's important to note that, despite these variations, a consistent association between muscle loss and dysphagia was observed.

Dysphagia is well-documented as a consequence of age-related muscle wasting, known as sarcopenia20. Given that the mean ages in these studies ranged from 66 to 70, and the estimated prevalence of sarcopenia in patients aged 65 to 70 is around 14% [26], it's reasonable to consider that some patients might have experienced dysphagia due to sarcopenic muscle loss rather than cachexia. This is plausible, especially since only one of the selected studies took sarcopenia into account [20]. Research is needed to explore how the interplay between the cachectic mechanism of inflammatory muscle destruction and sarcopenic muscle loss impacts these associations, emphasizing the importance of controlling for sarcopenia in future studies.

The potential link between cancer cachexia and dysphagia suggests that markers of cachexia may signal the need for dysphagia assessment in patients with non-head and neck tumours. Unlike other muscle-wasting conditions like sarcopenia, there's evidence to indicate that cachexia is not associated with neuromuscular junction pathology [27]. In the absence of denervation, muscle weakness in cachexia might be solely attributed to intrinsic muscle degradation. If this holds true, the extent of skeletal muscle loss in cancer cachexia patients could directly indicate their dysphagia risk.

LIMITATIONS

This systematic literature review has several limitations. The requirement that the term "cancer" or related words be in the title of each paper may have excluded potentially relevant articles. The exclusion of non-English papers, pre-prints, and grey literature also raises the risk of missing pertinent studies. The lack of a second independent reviewer may introduce bias. The heterogeneity among the included papers, particularly Wakabayashi et al., 2015, which examined skeletal muscle index instead of cachexia, posed significant limitations. The use of odds ratios and prevalence reports made comparisons challenging. The studies had different designs: one case-control, two cross-sectional, and one analysis of previously reported cohort data. The use of varying CASP tools for cohort and case-control studies limited the strength of quality comparison.

CONCLUSION

The aim of this review was to explore the links between cancer cachexia and dysphagia in patients with tumours beyond the head and neck. Swallowing problems are common in cancer patients, yet they are often overlooked in non-head and neck cancers. This oversight can negatively impact patients' quality of life and increase mortality rates. The data gathered in this review suggest that cachexia is independently associated with dysphagia in cancer patients. While factors like sarcopenia, neurodegenerative diseases, or bias might contribute to these associations, there is a consistent trend in these studies. This review paves the way for future research into the mechanisms of cachexia-related dysphagia and their interactions with sarcopenia. The evidence also supports the use of cachexia-related muscle loss measures as indicators of dysphagia risk in patients with tumours outside the swallowing regions. Ultimately, a greater focus on this condition will enhance the early identification and management of dysphagia.

References

1. Dysphagia - Guidance. RCSLT. (2021). Retrieved March 17, 2022, from https://www.rcslt.org/members/clinical-guidance/dysphagia/dysphagia-guidance/#section-2
2. Cock, C., & Omari, T. (2017). Diagnosis of swallowing disorders: How we interpret pharyngeal manometry. Current Gastroenterology Reports, 19(3). https://doi.org/10.1007/s11894-017-0552-2
3. Hutcheson, K. A., Lewin, J. S., Barringer, D. A., Lisec, A., Gunn, G. B., Moore, M. W. S., & Holsinger, F. C. (2012). Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer, 118(23), 5793–5799. https://doi.org/10.1002/cncr.27631
4. Raber-Durlacher, J. E., Brennan, M. T., Verdonck-de Leeuw, I. M., Gibson, R. J., Eilers, J. G., Waltimo, T., Bots, C. P., Michelet, M., Sollecito, T. P., Rouleau, T. S., Sewnaik, A., Bensadoun, R.-J., Fliedner, M. C., Silverman, S., & Spijkervet, F. K. (2011). Swallowing dysfunction in cancer patients. Supportive Care in Cancer, 20(3), 433–443. https://doi.org/10.1007/s00520-011-1342-2
5. Frowen, J., Hughes, R., & Skeat, J. (2019). The prevalence of patient-reported dysphagia and oral complications in cancer patients. Supportive Care in Cancer, 28(3), 1141–1150. https://doi.org/10.1007/s00520-019-04921-y
6. Panebianco, M., Marchese-Ragona, R., Masiero, S., & Restivo, D. A. (2020). Dysphagia in neurological diseases: A literature review. Neurological Sciences, 41(11), 3067–3073. https://doi.org/10.1007/s10072-020-04495-2

7. Nguyen, N. P., Vos, P., Moltz, C. C., Frank, C., Millar, C., Smith, H. J., Dutta, S., Alfieri, A., Lee, H., Martinez, T., Karlsson, U., Nguyen, L. M., & Sallah, S. (2008). Analysis of the factors influencing dysphagia severity upon diagnosis of head and neck cancer. The British Journal of Radiology, 81(969), 706–710. https://doi.org/10.1259/bjr/98862877
8. Szczesniak, M. M., Maclean, J., Zhang, T., Graham, P. H., & Cook, I. J. (2014). Persistent dysphagia after head and neck radiotherapy: A common and under-reported complication with significant effect on non-cancer-related mortality. Clinical Oncology, 26(11), 697–703. https://doi.org/10.1016/j.clon.2014.08.009
9. King, S. N., Dunlap, N. E., Tennant, P. A., & Pitts, T. (2016). Pathophysiology of radiation-induced dysphagia in head and neck cancer. Dysphagia, 31(3), 339–351. https://doi.org/10.1007/s00455-016-9710-1
10. Teunissen, S. C. C. M., Wesker, W., Kruitwagen, C., de Haes, H. C. J. M., Voest, E. E., & de Graeff, A. (2007). Symptom prevalence in patients with incurable cancer: A systematic review. Journal of Pain and Symptom Management, 34(1), 94–104. https://doi.org/10.1016/j.jpainsymman.2006.10.015
11. Fearon, K., Strasser, F., Anker, S. D., Bosaeus, I., Bruera, E., Fainsinger, R. L., Jatoi, A., Loprinzi, C., MacDonald, N., Mantovani, G., Davis, M., Muscaritoli, M., Ottery, F., Radbruch, L., Ravasco, P., Walsh, D., Wilcock, A., Kaasa, S., & Baracos, V. E. (2011). Definition and classification of Cancer cachexia: An international consensus. The Lancet Oncology, 12(5), 489–495. https://doi.org/10.1016/s1470-2045(10)70218-7
12. Argilés, J. M., Busquets, S., Stemmler, B., & López-Soriano, F. J. (2014). Cancer cachexia: Understanding the molecular basis. Nature Reviews Cancer, 14(11), 754–762. https://doi.org/10.1038/nrc3829
13. Giordano, A., Calvani, M., Petillo, O., Carteni', M., Melone, M. R., & Peluso, G. (2003). Skeletal muscle metabolism in physiology and in cancer disease. Journal of Cellular Biochemistry, 90(1), 170–186. https://doi.org/10.1002/jcb.10601
14. Ross, P. J., Ashley, S., Norton, A., Priest, K., Waters, J. S., Eisen, T., Smith, I. E., & O'Brien, M. E. (2004). Do patients with weight loss have a worse outcome when undergoing chemotherapy for lung cancers? British Journal of Cancer, 90(10), 1905–1911. https://doi.org/10.1038/sj.bjc.6601781
15. Couch, M., Lai, V., Cannon, T., Guttridge, D., Zanation, A., George, J., Hayes, D. N., Zeisel, S., & Shores, C. (2007). Cancer cachexia syndrome in head and neck cancer patients: Part I. diagnosis, impact on quality of life and survival, and treatment. Head & Neck, 29(4), 401–411. https://doi.org/10.1002/hed.20447
16. Arthur, S. T., Noone, J. M., Van Doren, B. A., Roy, D., & Blanchette, C. M. (2014). One-year prevalence, comorbidities and cost of cachexia-related inpatient admissions in the USA. Drugs in context, 3, 212265. https://doi.org/10.7573/dic.212265
17. Okuni, I., Otsubo, Y., & Ebihara, S. (2021). Molecular and neural mechanism of dysphagia due to cancer. International Journal of Molecular Sciences, 22(13), 7033. https://doi.org/10.3390/ijms22137033
18. Kenny, C., Regan, J., Balding, L., Higgins, S., O'Leary, N., Kelleher, F., McDermott, R., Armstrong, J., Mihai, A., Tiernan, E., Westrup, J., Thirion, P., & Walsh, D. (2019). Dysphagia prevalence and predictors in cancers outside the head, neck, and upper gastrointestinal tract. Journal of Pain and Symptom Management, 58(6). https://doi.org/10.1016/j.jpainsymman.2019.06.030
19. Amano, K., Morita, T., Koshimoto, S., Uno, T., Katayama, H., & Tatara, R. (2018). Eating-related distress in advanced cancer patients with Cachexia and family members: A survey in palliative and supportive care settings. Supportive Care in Cancer, 27(8), 2869–2876. https://doi.org/10.1007/s00520-018-4590-6
20. Lasheen, W., & Walsh, D. (2009). The cancer anorexia-cachexia syndrome: Myth or reality? Supportive Care in Cancer, 18(2), 265–272. https://doi.org/10.1007/s00520-009-0772-6
21. Wakabayashi, H., Matsushima, M., Uwano, R., Watanabe, N., Oritsu, H., & Shimizu, Y. (2015). Skeletal muscle mass is associated with severe dysphagia in cancer patients. Journal of Cachexia, Sarcopenia and Muscle, 6(4), 351–357. https://doi.org/10.1002/jcsm.12052
22. Tamura, F., Kikutani, T., Tohara, T., Yoshida, M., & Yaegaki, K. (2012). Tongue thickness relates to nutritional status in the elderly. Dysphagia, 27(4), 556–561. https://doi.org/10.1007/s00455-012-9407-z
23. White, G. N., O'Rourke, F., Ong, B. S., Cordato, D. J., & Chan, D. K. (2008). Dysphagia: causes, assessment, treatment, and management. Geriatrics, 63(5), 15–20.
24. Kunieda, K., Ohno, T., Fujishima, I., Hojo, K., & Morita, T. (2013). Reliability and validity of a tool to measure the severity of dysphagia: The Food Intake Level Scale. Journal of Pain and Symptom Management, 46(2), 201–206. https://doi.org/10.1016/j.jpainsymman.2012.07.020
25. Crary, M. A., Mann, G. D., & Groher, M. E. (2005). Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. Archives of Physical Medicine and Rehabilitation, 86(8), 1516–1520. https://doi.org/10.1016/j.apmr.2004.11.049
26. Santilli, V. (2014). Clinical definition of sarcopenia. Clinical Cases in Mineral and Bone Metabolism. https://doi.org/10.11138/ccmbm/2014.11.3.177
27. Boehm, I., Miller, J., Wishart, T. M., Wigmore, S. J., Skipworth, R. J. E., Jones, R. A., & Gillingwater, T. H. (2020). Neuromuscular junctions are stable in patients with cancer cachexia. Journal of Clinical Investigation, 130(3), 1461–1465. https://doi.org/10.1172/jci128411

Supplementary

Appendix 1: Sample Data Extraction Table

Bibliographical Information *(Title, author, year of publication, funding)*	**Objectives**	**Study Design + Methodology** (Sample size, inclusion/exclusion criteria, recruitment method)	**Exposure** *(Patient characteristics, cancer type & stage, other complications (e.g. dementia), treatments, setting, cachexia definition)*	**Outcome** *(Dysphagia definition, associated outcomes)*	**Results** *(relative risk and odds ratios)*	**Strengths and Limitations**
(Amano et al., 2018) **Eating-related distress in advanced cancer patients with cachexia and family members: a survey in palliative and supportive care settings** **Funding**: The Institutional Review Board approved this study (No. 1804008)	[1] to examine the severity of nutrition impact symptoms, which are to be palliated as part of nutritional support, in advanced cancer patients and the prevalence of eating-related distress among patients and their family members in palliative and supportive care settings, including outpatient services, palliative and supportive care teams, and the palliative care unit [2] compared these parameters between the following groups: (1) non-cachexia/pre-cachexia and (2) cachexia/refractory cachexia.	Type: Cross-sectional Population: Palliative care patients in Osaka City General Hospital (advanced cancer patients) Sample Size: N= 140 Recruitment Method: Primary palliative care physicians consecutively identified potential participants among patients, researchers approached patients and families and delivered questionnaires. If response was given, this was consent. Inclusion Criteria: (1) adult patients receiving palliative care, (2) patients diagnosed with locally extensive or metastatic cancer (including haematological neoplasms), (3) Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–3, 4) no marked fluid retention, e.g., ascites, pleural effusion, and peripheral oedema, (5) capable of replying to a self-reported questionnaire, (6) awareness of the diagnosis of malignancy, and (7) no serious psychological distress recognized by the primary palliative care physician's interview Family members: 1) primary caregivers of patients meeting the inclusion criteria as above, (2) capable of replying to a self-reported questionnaire, (3) awareness of the diagnosis of malignancy, and (4) no serious psychological distress recognized by the primary palliative care physician's interview. Exclusion Criteria: - Methods: - Eating-related distress questionnaire - 9 symptoms evaluated: pain, tiredness, drowsiness, nausea, lack of appetite, shortness of breath, depression, anxiety, and a feeling of well-being (ESAS-r tool) - Split into non/pre-cachexia and cachexia/refractory groups	Mean age: 66.3 (±11.1) Primary cancer types included esophageal (n = 55), lung (n = 13), gastric (n = 11), brain (n = 6), colon (n = 5), prostate (n = 5), hepatocellular (n = 2), thyroid (n = 2), pharyngeal (n = 2) and others (n = 10) Disease Extent: Metastatic n=484 (100%) Treatment Status: Pre-chemotherapy 8 (5.7%) Chemotherapy 89 (63.6%) Never treated/previous treatment 43 (30.7%) **Cachexia Definition**: (Fearon et al., 2011) Cachexia/refractory cachexia was a body weight loss rate (BWLR) in 6 months ≥ 5% or body mass index (BMI) < 20 kg/m2 + BWLR in 6 months ≥ 2%.	**Dysphagia Definition**: ➔ *Difficulty Swallowing* *Bauer J, Capra S, Ferguson M (2002) Use of the scored patient-generated subjective global assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. Eur J Clin Nutr 56(8):779–785*	**0 (0-2)** *[P=0.002]* *Non-cachexia patients presenting with dysph* **2 (0-5)** *[P=0.002]* *Cachexia/refractory patients presenting with dysph* ***Conclusions**:* *(Another study saw dysphagia in 12% of patients with cancer cachexia)* • *"Patients with cachexia had significantly greater eating-related distress than those without cachexia."* • *"In addition, the present study showed that the severity of 8 symptoms, i.e., tiredness, drowsiness, lack of appetite, early satiety, diarrhea, abnormal taste, difficulty swallowing, and feeling of well-being, were significantly greater in the cachexia/refractory cachexia group"*	**Strengths**: • Validated definition of cachexia **Limitations**: • Body weight measurements may have underestimated the frequency of cancer cachexia in patients who had gained weight due to fluid retention and overestimated it in overweight or obese patients • Items related to distress originating from the relationship between patients and their families may have been underestimated • A main limitation is that the measures for eating-related distress in both advanced cancer patients and their family members have not been previously validated

The Cancer Anorexia-Cachexia Syndrome: Myth or Reality? *(Lasheen and Walsh., 2010)*	
1. Did the study address a clearly focused issue?	Yes. It is unclear how to define CACS and if it is a distinct clinical disorder. The researchers evaluated whether CACS is a distinct clinical entity, identified the clinical features and assessed their impact
2. Was the cohort recruited in an acceptable way?	Yes. These participants are representative of the palliative care cancer patient population. The participants were not recruited, as this is a post hoc analysis of a cohort. This is however an acceptable method given that the data is all present for a reasonable proportion of this cohort. Only symptoms with an overall prevalence of over 5% were analysed, which limited the exclusion of patients without uncommon symptoms.
3. Was the exposure accurately measured to minimise bias?	Yes. Self-reported weight measurements were confirmed by medical documentation. Appropriate definition of cachexia was used, with over 10% weight loss being used in other studies. The study was produced before the international consensus on cachexia definition but employs a frequently used cachexia definition at this time.
4. Was the outcome accurately measured to minimise bias?	Can't tell. "Data was collected using an eight-page questionnaire". The validity or reliability of this questionnaire is not addressed. Even within the paper that originally reported these data, there is no indication that this is a validated diagnosis of dysphagia. The questionnaire was "empirically derived", however its specificity with regards to dysphagia is questionable.
5. (a) Have the authors identified all important confounding factors?	Yes. Primary cancer site and a number of other contributing variables are mentioned in the statistical analyses.
5. (b) Have they taken account of the confounding factors in the design and/or analysis?	Yes. Regression was performed with age, gender, ECOG, primary cancer site, group CACS, group A, group WL, and group N.
6. (a) Was the follow up of subjects complete enough?	n/a
6. (b) Was the follow up of subjects long enough?	n/a
7. What are the results of this study?	Dysphagia significantly more common in the CACS group when compared to group A and group WL ($P<0.01$).
8. How precise are the results?	Can't tell. The results all have a precise p-value (all $p<0.05$). Confidence intervals are not given.
9. Do you believe the results?	Yes. The p-value is low, and confounders have been accounted for. The study methods are solid and should support the accuracy of these results.
10. Can the results be applied to the local population?	Can't tell. The questionnaire used by the study is not clear and therefore may not be validated or accessible for other populations. Cachexia definition should be applicable to local populations; however the international consensus may serve as a more reliable measure of cachexia.
11. Do the results of this study fit with other available evidence?	Yes. conditions and dysphagia, however, this paper does not focus on the mechanism involved in its discussion section.
12. Does the study have implications for practice?	Yes. More research is needed to distinguish this syndrome. A comprehensive validated CACS assessment instrument is required in the future. This study suggest that CACS is a subset of cachexia and includes 9 other symptoms (which could in fact be caused by cachexia itself however).

Appendix 3: Sample Quality Appraisal – CASP Case Control Checklist

Skeletal muscle mass is associated with severe dysphagia in cancer patients (Wakabayashi et al., 2015)	
1. Did the study address a clearly focused issue?	Yes. No studies have reported the association between skeletal muscle mass assessed by abdominal CT and severe dysphagia. Focus is justified.
2. Did the authors use an appropriate method to answer their question?	Yes. Appropriate method of identifying the relationship, as researchers can identify those with and without dysphagia by means of clinical assessment and determine the effects if exposures from here
3. Were the cases recruited in an acceptable way?	Yes. Cases were identified by their diagnosis of cancer and referral for speech therapy to treat dysphagia by Yokohama City University Medical Center. These are representative of cancer patients admitted to this medical center. All patients who fitted the cancer and dysphagia rehabilitation criteria where included. The exclusion of patients who had undergone CT for diagnostic purposes is justified. No selection bias is evident through this approach. Cases were diagnosed for accuracy.
4. Were the controls selected in an acceptable way?	Yes. Controls were recruited in the exact same method as above and were defined as those who did not have dysphagia at the time of discharge. This was the only differentiating factor about the controls.
5. Was the exposure accurately measured to minimise bias?	Yes. Skeletal muscle mass was measured appropriately by CT. Measurements were consistent with cases and controls.
6. (a) Aside from the experimental intervention, were the groups treated equally?	Yes. Patients were all subject to the same measurement procedures. They are all admitted to the same hospital and referral scheme, however socio-economic factors are no investigated.
6. (b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Yes. Skeletal muscle index was associated with dysphagia after adjustment for age, gender, serum albumin, haemoglobin, cancer type and stage and vocal cord paralysis. This negates factors which may have caused dysphagia.
7. How large was the treatment effect?	Moderate. Forced entry logistic regression analysis showed that the skeletal muscle index (odds ratio [OR] 1.829; 95% confidence interval [CI]1.107–3.022; P = 0.018) was associated independently with oral food intake at discharge. The only significant adjustment was BMI, which made a difference of 0.508 to the OR [P<0.05] which is somewhat related to skeletal muscle mass. However the association was still significant outside of this.
8. How precise was the estimate of the treatment effect?	Can't tell. Relatively narrow CI intervals, however P values only
9. Do you believe the results?	Yes. All potential confounders are accounted for (bar cachexia, which is itself related to skeletal muscle mass and therefore linked). Associations are relatively strong and possible mechanisms are explored in the discussion to back up findings.
10. Can the results be applied to the local population?	Yes. Similar measurements could be performed in a local setting, provided the participants can be recruited by means of referral.
11. Do the results of this study fit with other available evidence?	Yes. The findings are supported by other papers as discussed in the discussion section.