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REVIEW

Managing Cachexia in Head and Neck Cancer: a Systematic Scoping Review

Antti A. Mäkitie · Rasheed Omobolaji Alabi · Helena Orell · Omar Youssef · Alhadi Almangush · Akihiro Homma · Robert P. Takes · Fernando López · Remco de Bree · Juan P. Rodrigo · Alfio Ferlito

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ABSTRACT

Introduction: Patients with head and neck cancer (HNC) are usually confronted with functional changes due to the malignancy itself or its treatment. These factors typically affect important structures involved in speech, breathing, chewing, swallowing, and saliva production. Consequently, the intake of food

will be limited, which further contributes to loss of body weight and muscle mass, anorexia, malnutrition, fatigue, and anemia. This multifactorial condition can ultimately lead to cancer cachexia syndrome. This study aims to examine the treatment of cachexia in HNC patients.

Methods: We systematically searched OvidMedline, PubMed, Scopus, and Web of Science for articles examining the treatment of cachexia in HNC.

Results: A total of nine studies were found, and these suggested interventions including nutritional, pharmacologic, therapeutic exercise, and

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multimodal approaches. The nutritional intervention includes essential components such as dietary counseling, oral nutritional supplements, and medical nutritional support. Individualized nutritional interventions include oral, enteral (feeding tubes i.e., percutaneous endoscopic gastrostomy [PEG], nasogastric tube [NGT]) and parenteral nutrition. The pharmacologic interventions aim at increasing the appetite and weight of cachectic patients. Therapeutic exercise and increased physical activity can help to enhance the synthesis of muscle protein, reducing inflammation and the catabolic effects of cachexia syndrome.

Conclusion: Owing to the multifactorial nature of this syndrome, it is expected that the management approach should be multi-interventional. Early implementation of these interventions may help to improve survival and quality of health and life of cachectic HNC patients.

Keywords: Anorexia; Cachexia; Head and neck cancer; Systematic review; Sarcopenia

Key Summary Points

Head and neck cancer (HNC) patients frequently suffer from cachexia, which is a multifactorial condition that can affect the treatment outcome and quality of life of these patients.

The management approach of HNC-related cachexia should be multi-interventional because of the multifactorial nature of the syndrome.

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The optimal approach would include preventive measures and early diagnosis of this condition. Additionally, novel technology carries the potential to aid in recognizing and monitoring early signs of cachexia.

Awareness of this entity (cachexia) needs to be raised among both surgical and oncologic caregivers. To perform the required clinical research, the standard for clinically applicable score for cachexia classification and assessment should be defined.

In the future, individualized treatment options that can be offered for this patient population should be explored.

INTRODUCTION

Cancer may be associated with pain, psychological distress, disfiguration, dysfunction, malnutrition, metabolic changes, and ultimately death [1]. It is the second leading cause of death worldwide and can affect any part of the body including the head and neck region [2]. In the USA, head and neck cancer (HNC) accounts for 3% of new cases for all cancers and 1.5% of all cancer deaths [3, 4]. Furthermore, HNC was ranked as one of the most common cancers globally in 2018 [1].

Several recent advancements in the treatment planning and management of HNC include minimally invasive procedures, transoral robotic surgery, organ-sparing surgical procedures, advancements in radiotherapy, and curative multimodal treatment including immune-checkpoint inhibitors [1]. All of these are targeted at reducing morbidity, mortality, and physical and psychologic changes while preserving the daily function that can enhance improved quality of life of HNC patients. HNC patients frequently suffer from dysphagia and anorexia because of the tumor growth itself and/or treatment-related side effects or anxiety as to the possible outcome of treatment [5]. Consequently, malnourishment and weight loss

Table 1 Main findings in the included studies

Study/type of study	Location	Title of the study	Size of the series (methodology)	Intervention	Conclusion
Mantovani et al. [23]/original study ^a	Italy	A phase II study with antioxidants, both in the diet and as supplemented pharmaconutritional support, progesterone, and anti/cyclooxygenase-2 showing efficacy and safety in patients with cancer-related anorexia/cachexia and oxidative stress	39	Integrated treatment: Pharmaconutritional support	Body weight, lean body mass, and appetite increased significantly Improved quality of life The intervention was effective and safe
Lai et al. [24]/original study	US	Results of a pilot study of the effects of celecoxib on cancer cachexia in patients with cancer of the head, neck, and gastrointestinal tract	11 (4 for celecoxib-treated patients, 7 for placebo-treated patients)	Pharmacologic intervention—celecoxib	Patients that received celecoxib experienced noticeable increase in weight and body mass index The weight and body mass index in the placebo group decreased A moderate dose of celecoxib for cachectic patients may help in the quest to manage cachexia and improve quality of life score in cancer cachectic patients. This approach may also improve the outcome of cancer therapy

Table 1 continued

Study/type of study	Location	Title of the study	Size of the series (methodology)	Intervention	Conclusion
Mantovani et al. [25]/ randomized controlled trial ^a	Italy	Randomized phase III clinical trial of five different arms treatment in 332 patients with cancer cachexia	332 Arm 1 (n = 44): patients received medroxyprogesterone Arm 2 (n = 25): patients were given oral supplement Arm 3 (n = 88): only L-carnitine was given to the patients Arm 4 (n = 87): thalidomide was given to the patients Arm 5 (n = 88): combination of the above-mentioned arms	Pharmacologic intervention— Medroxyprogesterone, megestrol acetate, L-carnitine, thalidomide Nutritional intervention— oral supplement with eicosapentaenoic acid Multi-interventional— combination of the aforementioned pharmacologic and nutritional interventions	Patients that received multi-interventional treatment (arm 5) showed the best treatment outcome
Madeddu et al. [26]/ randomized controlled trial ^a	Italy	Randomized phase III clinical trial of a combined treatment with carnitine + celecoxib ± megestrol acetate for patients with cancer-related anorexia/cachexia syndrome	60	Pharmacologic intervention—1. Arm (1) two-drug combination. Arm (2) two-drug combination + megestrol acetate Antioxidants	There was no significant difference between the two arms

Table 1 continued

Study/type of study	Location	Title of the study	Size of the series (methodology)	Intervention	Conclusion
Yeh et al. [27]/ original article	Taiwan	Omega-3 fatty acid, micronutrient, and probiotic-enriched nutrition helps body weight stabilization in head and neck cancer cachexia	68 (31 patients received Ethanwell regimen, 37 patients received Isocal)	Nutritional intervention—Omega-3 fatty acid, micronutrient, and probiotic-enriched nutrition	Increased body weight and higher serum albumin and pre-albumin were observed in patients that received Ethanwell
Grote et al. [28]/ randomized controlled trial	Germany	Progressive resistance training in cachectic head and neck cancer patients undergoing radiotherapy: a randomized controlled pilot feasibility trial	20 cachectic patients ($n = 10$ received machine-supported progressive resistance training, $n = 10$ received usual care)	Progressive resistance training is an exercise-oriented training The training took place 3 × in a week for 30 min	HNC patients with body mass index < 19 may benefit from EE regimen Progressive resistance training in cachectic HNC patients seems to be safe and posited to be beneficial for general fatigue and quality of life
Bar-Sela et al. [29]/ original study ^a	Israel	The effects of dosage-controlled cannabis capsules on cancer-related cachexia and anorexia syndrome in advanced cancer patients: pilot study	24 patients (17 started but 11 received capsules for more than 2 weeks)	Pharmacologic intervention	The cannabis capsule treatment led to increase in weight of the patients

Table 1 continued

Study/type of study	Location	Title of the study	Size of the series (methodology)	Intervention	Conclusion
Osmolak et al. [30]/ randomized controlled trial	USA	Does perioperative oxandrolone improve nutritional status in patients with cachexia related to head and neck carcinoma?	18 perioperative	Oxandrolone (perioperative administration of oxandrolone) Appropriate dose of oxandrolone for 10 days may be useful in perioperative care of nutritional deficiency in HNC patients	The perioperative administration of oxandrolone showed improvement in prealbumins level and subjective improvements in surgical wounds
Blum et al. [31]/a case series	Switzerland	Natural ghrelin in advanced cancer patients with cachexia, a case series	10 (6 received allocated intervention, 4 did not receive)	Nutritional intervention—ghrelin	Natural ghrelin has a positive effect on the nutritional intake of cachectic patients

^aAdvanced stage solid cancers including head and neck cancer

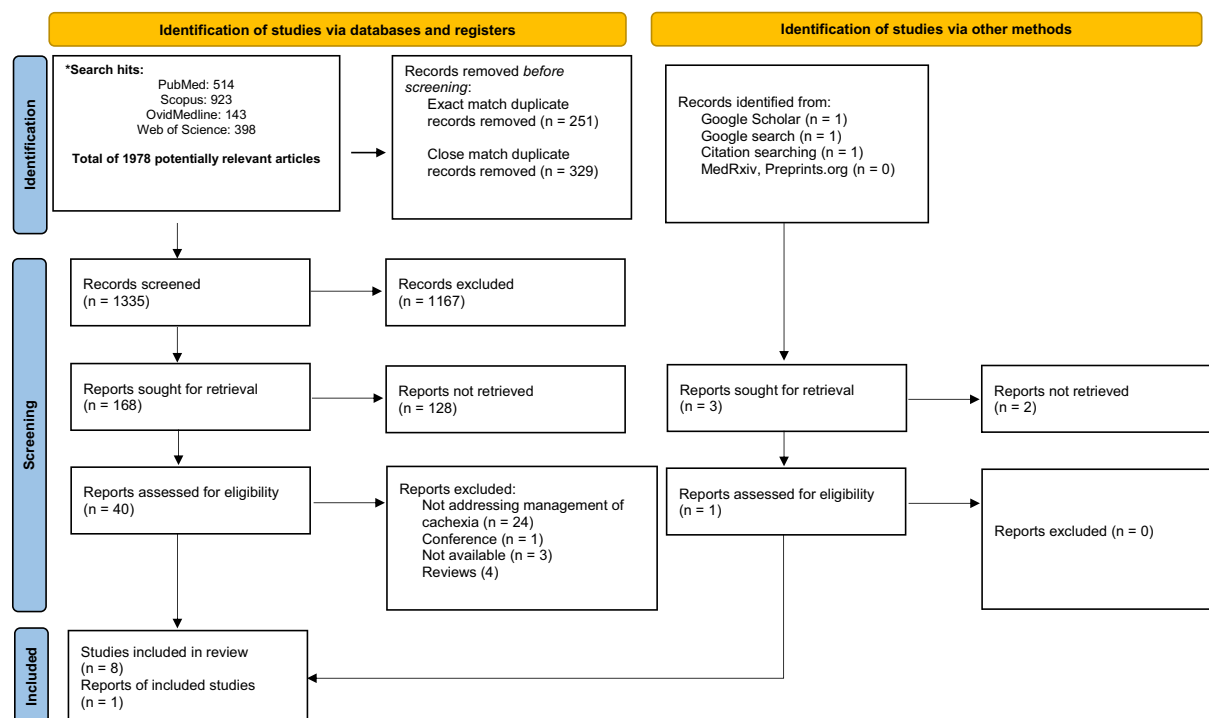


Fig. 1 PRISMA flow chart

are typically observed. Among HNC patients receiving radiotherapy (RT), severe weight loss was seen prior to RT in 3% and at the end of RT in 44% of patients, while the frequency of malnutrition increased from 3% up to 88% [6, 7].

Cachexia (or anorexia-cachexia syndrome) is a complex metabolic syndrome in which systemic inflammation is the key feature and weight loss (e.g., $\geq 5\%$ of body weight during the past 6 months) is the key diagnostic criterion. Cachexia can be an underlying condition in patients with sarcopenia. Anorexia is characterized by decreased food intake because of treatment side effects and depression, and it manifests as reduced energy intake and involuntary weight loss in these patients [5]. Cachexia can be defined as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Cachexia is primarily associated with a particular underlying condition such as uncontrollable tumor

growth that leads to extreme loss of appetite and weight and systemic signs of inflammations [5, 8–11]. When it affects oncologic patients, it is known as cancer cachexia (cancer-induced cachexia) [12]. In this case, there is a loss of appetite due to metabolic alterations associated with cancer. Thus, the quality of life and health of these patients are affected due to the cancer itself and increased by treatment-related toxicity [13] causing poor survival [14]. Weight loss can be associated with loss of muscle mass and function (e.g., strength), and this is referred to as sarcopenia. Sarcopenia was first thought to be a physiologic state in the elderly; however, scientific research has changed the perception of the condition and uncovered myriad causes. Sarcopenia can be the result of cancer cachexia, and it has been associated with adverse treatment outcome in HNC patients [15].

Among HNC patients, cachexia is more pronounced as this cancer affects the functional structures of the human body that are directly involved in nutritional intake. As a result, deglutitive and masticatory functions are affected resulting in a deterioration of nutritional status.

Table 2 Summary of quality assessment using the Oxford quality scoring system (Jadad scale)

Study	Oxford quality scoring system	Quality interpretation
Mantovani et al. [23]	3	High
Lai et al. [24]	5	High
Mantovani et al. [25]	4	High
Madeddu et al. [26]	5	High
Yeh et al. [27]	5	High
Grote et al. [28]	4	High
Bar-Sela et al. [29]	2	Low
Osmolak et al. [30]	3	High
Blum et al. [31]	3	High

In addition, patients may become vulnerable to infection, fatigue, pain, and dyspnea. All these may contribute further to weight loss and have a negative effect on functional and survival prognoses [16]. As sarcopenia is primarily a functional condition, the patients with cachexia experience negative changes in metabolic functioning, loss of appetite, loss of adipose tissue, wasting of tissues, and loss of skeletal muscle mass.

We systematically reviewed the published studies on the treatment of cachexia in HNC. It was our primary aim to explore the scientific evidence on the preventive approaches and management of cachexia in this patient population.

METHODS

Search of Databases and Study Period

We systematically searched OvidMedline, PubMed, Scopus, and Web of Science databases from inception until 15 October 2021 to retrieve all studies addressing cachexia in HNC.

Search Terms

The potentially relevant articles were retrieved by combining search keywords: [(‘cachexia OR sarcopenia’) AND (‘head and neck cancer’)].

Search Analysis

The search analysis was done using RefWorks web-based bibliography and database manager. All the retrieved potentially relevant articles were exported to RefWorks for further analyses. The hits were further analyzed for possible duplicates and irrelevant studies. The inclusion and exclusion criteria were defined based on the study-specific research questions.

Inclusion and Exclusion Criteria

All studies that had examined the treatment interventions of cachexia or sarcopenia in HNC were included. Considering the need to gather important information and to reduce research waste regarding cachexia and its management in head and neck cancer, systematic reviews on cachexia in HNC were included in this study. Furthermore, studies with no specific mention of a cancer site were considered in this review to check if they included general treatment interventions for cachexia. As the number of relevant studies appeared limited, a scoping review approach was applied. To minimize the omission of any potential study, the reference lists of all the potentially eligible articles were manually searched to ensure that all the relevant studies were adequately included. Comments, opinions, perspectives, guidelines, editorials, and articles in languages other than English were excluded. All articles about the

Table 3 Tool for assessing the risk of bias (adapted from Higgins et al. 2011)

Bias domain	Source of bias	Support for judgment
Selection bias	Random sequence generation	State how the cachectic patients were selected in sufficient detail to allow an assessment of whether it should produce comparable groups
	Allocation concealment	Describe the control group (groups that did not receive cachectic intervention) or compare between interventions in sufficient detail to determine whether intervention allocations were effective during enrollment
Performance bias	Blinding of participants ^a	State all measures used, if any, to prevent trial participants from having the knowledge of which intervention they received
Detection bias	Blinding of outcome assessment ^a	State all measures used, if any, to prevent influence of the knowledge of intervention received on the outcome assessment
Attrition bias	Incomplete outcome data ^a	Describe the completeness of outcome data for each endpoint, including incomplete and excluded participants from the analysis
Reporting bias	Selective reporting	State how the endpoint reporting was done and what was the conclusion
Other biases	Anything else, ideally prespecified	Other biases not covered elsewhere in the examined domains. For example, the inclusion of other tumors besides head and neck cancer in the analysis

^aAssessments made for each main outcome (endpoint)

Table 4 Presentation of risk of bias assessments for the included studies

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other biases
Mantovani et al., 2006	●	●	●	●	●	●	●
Lai et al., 2008	●	●	●	●	●	●	●
Mantovani et al., 2010	●	●	●	●	●	●	●
Madeddu et al., 2012	●	●	●	●	●	●	●
Yeh et al., 2013	●	●	●	●	●	●	●
Grote et al., 2018	●	●	●	●	●	●	●
Bar-Sela et al., 2019	●	●	●	●	●	●	●
Osmolak et al., 2019	●	●	●	●	●	●	●
Blum et al., 2021	●	●	●	●	●	●	●

Low risk ● Unclear risk ● High risk ●

Table 5 Included studies and the examined endpoints

S/ N	Studies	Examined endpoints	Intervention	Duration of intervention	Results
1	Mantovani et al. [23]/ original study ^a	Body weight Lean body mass	Pharmacologic intervention	12 weeks	500 mg/day medroxyprogesterone acetate; 200 mg/day celecoxib; 2.2 g/day eicosapentaenoic acid or 0.9 g/day docosa hexaenoic acid; antioxidant These improved the following endpoints: Improved quality of life Increased appetite
2	Lai et al. [24]/ original study	Body weight Body mass index Quality of life	Pharmacologic intervention— celecoxib	21 days	Patients that received celecoxib showed: Increase in body weight Increase in body mass index Increased quality of life score
3	Mantovani et al. [25]/ original study ^a	Primary endpoints: Lean body mass Decrease in resting energy expenditure Decrease in fatigue Secondary endpoints: Appetite Quality of life Grip strength	Pharmacologic intervention— Nutritional intervention Hybrid regimen: combination of pharmacologic and nutritional interventions	4 months	A combination of 500 mg/day of medroxyprogesterone or 320 mg/day + oral supplement with eicosapentaenoic acid + 4 g/day of L- carnitine + 200 mg/day of thalidomide improved the following endpoints: Improved lean body mass Increased appetite Interleukin (IL)—6 decreased significantly Toxicity reduced

Table 5 continued

S/ N	Studies	Examined endpoints	Intervention	Duration of intervention	Results
4	Madeddu et al. [26]/ original study ^a	Primary endpoints: Lean body mass Physical activity Secondary endpoints: Physical performance Grip strength Walk test	Pharmacologic intervention	4 months	4 g/day L-carnitine + 300 mg/day celecoxib ± 320 mg/day megestrol acetate Improved physical function Fatigue Improved performance Appetite
5	Yeh et al. [27]/ original study	Body weight Serum albumin level Albumin level	Nutritional intervention— ethanwell/ethanzyme (EE) regimen enriched with Omega-3 fatty acid, micronutrient, and probiotic-enriched nutrition or control (Isocal) for 3 months period	3 months	Patients with body mass index < 19 showed improved body weight Higher serum albumin levels Higher prealbumin level The increase in body weight was associated with increased serum albumin and prealbumin level
6	Grote et al. [28]/ randomized controlled trial	Fatigue (body weight) Quality of life	Exercise (progressive resistance training)	15 weeks (7 weeks of radiotherapy and 8 weeks after radiotherapy)	Less fatigue was observed Improved quality of life

Table 5 continued

S/ N	Studies	Examined endpoints	Intervention	Duration of intervention	Results
7	Bar-Sela et al. [29]/ original study ^a	Primary endpoints: Body weight Secondary endpoints: Appetite Reduction in pain and fatigue Grip strength	Pharmacologic intervention— (tetrahydrocannabinol and cannabidiol)	6 months	Weight increase of 10% in patients that received 5 mg × 1 or 5 mg × 2 capsules daily Improvement in appetite and mood Reduction in pain and fatigue
8	Osmolak et al. [30]/ randomized controlled trial	Prealbumin levels Surgical wounds	Nutritional intervention— oxandrolone	10 days	10 mg twice a day: Improvement in prealbumin levels Improvement in surgical wounds
9	Blum et al. [31]/a case series ^a	Muscle mass Appetite	Nutritional intervention— ghrelin	4 days (twice/day). Then, 6 weeks of maintenance period (10 doses/week)	32 µg/kg of body weight: improved appetite and eating-related symptoms Stable muscle mass and strength

^aAdvanced stage solid cancers including head and neck cancer

pathophysiology, pathogenesis, assessments, overview, effects, definitions, and diagnostic features of cachexia or sarcopenia were excluded. Similarly, studies that focused on anorexia, dysphagia, or mucositis, or mainly on nutritional support in cancer patients, were excluded. All studies that examined cachexia in animals were excluded.

Search Reporting and Screening

Two independent researchers (R.A. and O.Y) performed the screening of potentially relevant articles and used a data extraction sheet to

minimize the omission of possible eligible studies. Possible discrepancies were resolved by discussion until a consensus was reached. Thus, the interobserver reliability between the two independent researchers was measured using Cohen's kappa coefficient ($k = 0.94$). All eligible studies to be included are summarized in Table 1. The reporting of the search protocols (searching and screening processes) is given using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (Fig. 1). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and followed the PRISMA guidelines in the review process. As this study is a systematic

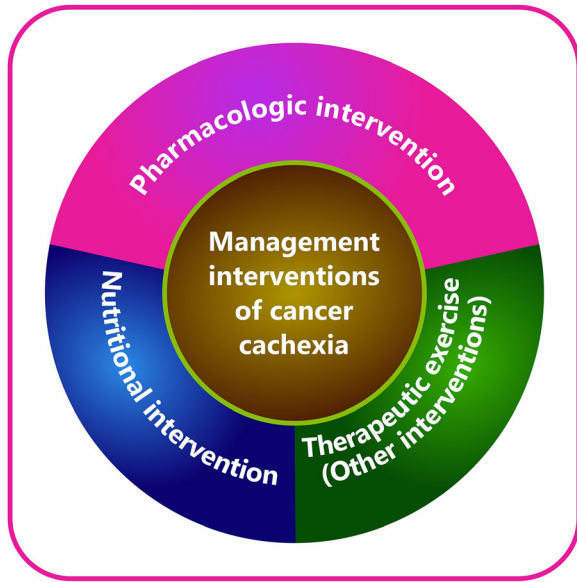


Fig. 2 Management interventions of cachexia

scoping review, ethical review and informed consent were not required.

Quality Appraisal

As this study considered original studies and randomized controlled trials as eligible studies, two different quality appraisal paradigms were

used. The quality of the included studies was initially appraised using the quality guideline for systematic review as recommended by the National Institute of Health Quality Assessment tools [17]. These studies were subjected to four quality criteria informed by the same quality assessment tool [18]. These criteria were modified to include design, methodology, interventions, and statistical analysis. The studies that showed reasonable quality ($\geq 50\%$) from this initial quality assessment were further subjected to the Oxford quality scoring system, also known as the Jadad scale. The Jadad quality assessment scale is a representative quality assessment tool that is suitable for systematic review that includes randomized controlled trails. It is an easy-to-use scale with known reliability and external validity and important elements that have empirically been shown to correlate with bias [19]. Based on this scale, the maximum attainable score was 5 points; two in relation to randomization, two in relation to blinding, and one in relation to the dropout rate [20, 21]. An overall score ≥ 3 indicated ‘high’ quality. Conversely, a Jadad scale score of ≤ 2 was defined as ‘low’ quality (Table 2) [20]. The quality assessment was followed by the risk of bias analysis of the included studies

Normal	Precachexia	Cachexia		Refractory cachexia	Mortality
	Anorexia	Low food intake	BMI of less than 20kg/m ²	Active metabolism	
	Metabolic change	Systemic inflammation	Lack of response to anti-cancer therapy	Low WHO performance status score of 3 or 4	
	Impaired glucose intolerance	Sarcopenia	Ongoing weight-loss of more than 2%	Significant unresponsiveness to anti-cancer therapy	
	Involuntary weight-loss [usually $\leq 5\%$]	Muscle depletion	More than 5% loss of stable body weight over the past 6 months	Lack of possibility of weight-loss management	
		Reduced anabolism	Alterations in lipids, protein, glucose, and energy metabolism	Life expectancy of less than 3 months	

Fig. 3 Understanding precachexia, cachexia, and refractory cachexia

using the Cochrane collaboration risk of bias tool (“Risk of Bias Analysis”).

Risk of Bias Analysis

We used the Cochrane Collaboration’s tool for assessing the risk of bias of the included studies. This tool was modified from Higgins et al. (2011) to properly examine the risk of bias in this study [22]. The modified bias domains appear summarized in Table 3. The details of the bias analysis and the corresponding results from each examined bias are presented in Table 4.

Data Extraction

In each eligible study, the first author’s name, year of publication, country, title of the study, number of the participants in the study or number of studies reviewed, site of cancer considered, suggested interventions or cachexia management, and summary of the study were extracted (summarized in Table 1). The detailed explanation of the strategic interventions to manage cancer cachexia in HNC patients is discussed collectively in the Discussion section. Based on the summary of the included studies (Table 1), the endpoints examined through randomized control trials, case series, and original studies included in this systematic scoping review are specifically discussed in this study and summarized in Table 5.

RESULTS

Results of the Database Search

A total of 1978 hits were retrieved. After deleting duplicates ($N = 580$), irrelevant papers ($N = 1357$), and exclusions ($N = 32$), we found nine studies eligible to be included in this scoping review as shown in Fig. 1 [23–31].

Characteristics of Relevant Studies

All the articles included were published in the English language. The quality assessment of the included studies showed that eight (88.9%)

showed high-quality assessment scores [23–28, 30, 31]. Likewise, only a single study (14.3%) of the included studies had a low-quality score (Table 2) [29]. In terms of the risk of bias, all the included studies showed low risk of bias in the selection of cachectic patients, analysis of the cachectic intervention and end-point evaluation, and reporting of outcome of these interventions (Table 4). Similarly, six out of the nine studies showed a low risk of unreliability of the examined interventions by comparing the outcome of the various intervention groups and those that received either placebo or no intervention at all [24–28, 30] (Table 4). However, only one study had a high risk of bias regarding the evaluated cachexia intervention because a reasonable number of the participants did not complete the study [29]. Additionally, four studies included other advanced stage solid cancers alongside head and neck cancer, which may include other biases in terms of the actual efficacy of the intervention [23, 25, 26, 29].

Of the nine included studies, five (55.6%) had been carried out in Europe [23, 25, 26, 28, 31] and two (22.2%) studies each in the US [24, 30] and Asia [27, 29]. From the included studies, two (22.2%) recommended both nutritional and pharmacologic interventions for the management of cachexia in HNC patients [23, 25]. Three (33.3%) studies each suggested only either nutritional intervention [27, 30, 31] or pharmacologic intervention [24, 26, 29]. Similarly, only one study (14.3%) suggested other emerging interventions in addition to the nutritional and pharmacologic interventions such as exercise or resistance training [28]. Of note, it was suggested that a multi-modal/multi-interventional approach that consists of pharmacologic, nutritional, and other targeted interventions is poised to be the most effective treatment in terms of the targeted endpoints of lean body mass, resting energy expenditure, fatigue, appetite, quality of life, and grip strength [25] (Fig. 2).

Summary of the Findings from the Relevant Studies

The findings of these studies (summarized in Table 1) indicate that cancer cachexia is associated with weight loss, poor nutritional status, and systemic inflammation. Cancer cachexia can thus predict a poor treatment outcome in patients with HNC. The primary endpoints examined for cachexia intervention in some of the included studies in this systematic scoping review were lean body mass, body weight, resting energy expenditure, fatigue, serum albumin level, prealbumin level, and body mass index [23–31] (Table 5). Likewise, the highlighted secondary endpoints for cachexia interventions were appetite, quality of life, reduction in pain, grip strength, physical performance, walk test, and surgical wounds [24–26, 28, 29, 31] (Table 5).

Hybrid regimens that include a combination of pharmacologic and nutritional interventions led to increase in lean body mass and decrease in resting energy expenditure and fatigue [25]. Similarly, hybrid regimens were also found to be potent interventions for cachectic endpoints of improved appetite, grip strength, and quality of life [25]. Besides hybrid interventions, pharmacologic interventions such as medroxyprogesterone, megestrol acetate, L-carnitine, celecoxib, thalidomide, tetrahydrocannabinol, and cannabidiol have shown promising results regarding their respective target endpoints of increased body weight, pain and fatigue reduction, improved grip strength, and improved quality of life [24, 25, 29]. Of note, only two of the pharmacologic interventions were found to be widely used and approved in Europe. These are progestational agents such as medroxyprogesterone acetate or megestrol acetate and corticosteroids [23, 25, 26, 32–35]. Similarly, some nutritional interventions such as ethanwell/ethanzyme regimen enriched with omega-3 fatty acids, micronutrients, and probiotics or control (isocal) were found to be effective in achieving the targeted endpoints of improved body weight, higher serum albumin and prealbumin levels, and improvement in surgical wound healing [27]. Other pharmaceutical interventions such as oxandralone was also

found to show improvements in prealbumin levels and surgical wound-healing endpoints of cachectic patients [30] while ghrelin was found to show improved appetite and provide stable muscle mass and strength endpoints [31] (Table 5). Some of the suggested interventions had been validated through clinical trials or randomized controlled trials [23, 25, 26, 28, 30] (Table 5).

Apart from the aforementioned randomized controlled trials that supported pharmacologic and nutritional interventions, other examples of pharmacologic and nutritional interventions were suggested in some studies, but had not yet been subjected to controlled trials. For pharmacologic interventions, these include growth hormone and anabolic steroids, non-steroidal anti-inflammatory drugs, TNF-alpha inhibitors, anticytokines, inflammatory antagonists, antioxidant agents, and selective androgen receptor modulators [32, 36–38]. For nutritional interventions, nutraceuticals, nutritional support, cyproheptadine, amino acid loading, curcumin, resveratrol, pomegranate, and other interventions such as physical activity were suggested [32, 36–38]. The use of pharmacologic interventions such as cyproheptadine, hydrazine, metoclopramide, and pentoxifylline was found to be ineffective in one study [39]. The interventional ability of some pharmaceutical drugs such as eicosapentaenoic acid, cannabinoids, and bortezomib was reported to have failed or produced equivocal results [39]. Thus, the discussion section of the present review focuses on interventions with promising results in the defined endpoints.

DISCUSSION

Cachexia is defined as a multifactorial syndrome characterized by the ongoing loss of skeletal muscle mass with loss of fat mass [11]. Nutritional support and therapy cannot fully reverse the condition of cachexia, and this will lead to reduced physical function [11]. It has been reported that higher energy intakes would be necessary in patients treated for HNC to maintain skeletal muscle mass [40]. Pathophysiologically, cachectic HNC patients have

reduced food intake and abnormal metabolism [11]. Precachexia is recognized by early clinical and metabolic signs that precede substantial weight loss, i.e., > 2% and < 5% [54]. This state is usually overlooked as an early stage of cachexia. It usually begins with a slight weight loss that occurs involuntarily. Nonetheless, metabolic changes and inflammations occur at this stage. While cachexia is the main condition considered in the present study, refractory cachexia is a clinically resistant catabolic state [10] (Fig. 3). Hence, it is a more severe syndrome with a low World Health Organization performance status score, an irresponsiveness to anticancer therapy, and a survival period of < 3 months [12] (Fig. 3).

A concerted effort is still ongoing to obtain a consensus on the diagnostic standard for refractory cachexia [10]. Of note, the patients progress from one stage to the other if timely and necessary interventions are not introduced [10] (Fig. 3). The chance of progression depends on factors such as the HNC subsite and stage, food intake, level of patient activity, irresponsiveness to anticancer treatment, and/or treatment-related sequelae and complications [10]. Therefore, early recognition of cachexia is important because cachectic patients have higher rates of postoperative complications and infections and impaired response to adjuvant treatment and thus poor quality of life and higher mortality rates [5, 41, 42]. Similarly, early initiation of aggressive nutrition intervention with multimodal approach improves outcomes by helping to maintain patient on the intended treatment regimen with fewer changes [43, 44]. Most importantly, cachexia syndrome should be taken into significant consideration for the effective development of practice guidelines, and ultimately, and routine clinical management of HNC patients.

Several attempts have been made to obtain unanimous consensus on a diagnostic benchmark for cancer cachexia [9, 11, 45]. The most widely presented criteria in the published studies include weight loss > 5% in the previous 6 months or weight loss > 2% in individuals already showing depletion according to current body mass index < 20 kg/m² or reduced skeletal muscle mass (sarcopenia) [11, 46]. Of note, it

has been observed that muscle mass depletion is common in HNC patients with cachectic syndrome [47].

Chemotherapeutic, radiotherapeutic, and surgical complications in HNC cachectic patients have resulted in a low survival rate [5]. Weight loss remains the primary reason, and it is one of the main features of a cachectic HNC patient. Thus, lowering the doses of (chemo)radiotherapy does not seem to be helpful for improving overall survival because of the severe weight loss [48, 49]. Therefore, weight loss has been found to be a detrimental factor hindering the proper management of cachectic HNC patients [5].

The generally accepted principal for the management of cachexia is based on early commencement of individualized nutrition with sufficient protein and energy intake with sufficient symptom management. Despite the advancements in diagnostic and treatment methods for HNC, little or no active attention is usually given to the recognition, assessment, and management of cachexia in this patient population [50–52]. Therefore, it seems to represent an unmet impending factor that can hinder maximizing the intended clinical benefits from multimodality treatment aimed at improving quality of health and chance of survival in HNC patients [53, 54]. Although cachexia has been well recognized as a disease condition, it deserves attention because of its potential to contribute to the mortality rate in patients with cancer [5].

This systematic review presents a scoping approach examining the published studies on management of cachexia in head and neck cancer (HNC) patients. The indices of cachexia include lean body mass, resting energy expenditure, fatigue, loss of appetite, reduced grip strength, inflammation, and impaired quality of life [25]. First, we found that cachexia has adverse effects on both functional (impaired quality of life and quality of health, increased healthcare expenses) and survival (cancer-related death) prognoses of cancer. Second, pharmacologic [24, 26, 29], nutritional [27, 30, 31], and therapeutic exercise (resistance training) [28] are the interventions suggested for managing cachexia in HNC patients (Fig. 2).

However, for optimal management of cachexia, a combination of these interventions, i.e., a multi-interventional approach, is recommended because of the multifactorial nature of the syndrome [23, 25, 32, 37–39, 55].

Considering weight loss as one of the indicators of cancer cachexia in HNC patients, nutritional interventions, including nutritional counseling and support, and supplemental interventions are poised to offer an effective management approach for this syndrome. For example, an oral nutrition supplement, like the ethanwell/ethanzyme (EE) regimen, which was enriched with omega-3 fatty acids, micronutrients, and probiotics, was found to enhance body weight stabilization in HNC cachectic patients [27]. The levels of serum albumin and pre-albumin in these patients were found to be significantly increased [27]. A similar study further emphasized the importance of a multi-targeted (multi-interventional) approach by combining dietary micronutrients such as omega-3 fatty acids with pharmacologic intervention. This combination was reported to improve fatigue and lean body mass [25].

The weight of HNC patients should be monitored and recorded during the disease trajectory for early detection of cachexia. Consequently, nutrition counseling by registered dietitian and individualized nutrition support aimed at improving weight loss and physical functions should be introduced. This will improve quality of health and aid in achieving the touted benefits from the cancer treatment. Because HNC and its treatment have the potential to affect the route of food intake, nutrition is usually administered to HNC patients through enteral route, i.e., percutaneous endoscopic gastrostomy (PEG), or nasogastric tube (NAG). Parenteral feeding is prescribed only for patients with nonfunctional or inaccessible enteral route [5]. This insightful approach to nutrition administration has been reported to help patients with less weight loss, improved quality of life, and survival rate [5, 25, 27, 56]. In addition, numerous guidelines have been suggested for the proper nutritional assessment, monitoring, and management of HNC cachectic patients [57]. Similarly,

numerous articles have been published on the importance of nutritional interventions [58].

Beyond the spectrum of nutritional intervention is pharmacologic intervention in the management of cachexia in HNC patients. This pharmacologic intervention can be divided into two main categories based on the intended aim of this intervention. First, these are drugs that increase appetite (i.e., appetite stimulants) in cachectic HNC patients. For instance, glucocorticoids, progestagens (medroxyprogesterone and megestrol acetate [megace]), glucocorticoids, and orexigenic agents (dronabinol, pentoxifylline, nandrolone, nutritional pharmacomodulation [omega-3 fatty acids], etc.) have been used to increase appetite in cachectic HNC patients [23, 27]. Second, other pharmacologic interventions include nonsteroidal anti-inflammatory and anticytokine drugs and antioxidant agents [5]. Examples of these drugs include celecoxib and thalidomide [5, 24, 26]. Of note, it is important to have a multimodal approach to these pharmacologic interventions to achieve the best outcomes [5, 23, 25]. Therefore, the onus is on the caregivers to evaluate the individualized situation of cachectic HNC patients for the best combination of pharmacologic therapy (multinutrient or multitarget) for improved body weight and appetite and reduced inflammation.

Therapeutic exercise and increased physical activity are thought to be beneficial for cachectic HNC patients [28, 59]. As cachexia is associated with inflammation and anemia, the potential of muscle pain and weakness increases. However, exercise therapy can help to enhance the synthesis of muscle protein. Additionally, it can reduce the catabolic effects of cachexia syndrome and the extent of inflammation. This is poised to offer a non-pharmacologic treatment of HNC cachectic patients to improve physical functions and quality of life [5, 28, 60]. Considering the condition of HNC cachectic patients, physical exercise may not be feasible. Thus, an alternative exercise paradigm such as neuromuscular electrical stimulation (NEMS) may be considered to strengthen the muscles [5].

This systematic scoping review emphasizes that the assessment and management of

cachexia in HNC patients constitute major challenges for clinicians [10]. The standard for a clinically applicable score for cachexia classification and assessment should be defined. The standard endpoints (primary and secondary) for cancer-induced interventions should be highlighted. Similarly, the assessment tool for these endpoints should be defined. The most effective interventional approaches should be properly evaluated. Even though there are neither effective medical interventions nor approved drugs to completely reverse cachexia [61], major caregivers such as oncologic nurses and clinicians have an important role in the proper management of cachectic HNC patients. For instance, an oncologic nurse should be vigilant for the early signs of cachexia for prompt intervention [5, 62]. This includes being active in the routine assessment of the dietary habits of patients, nutritional components (status, deficiencies, and possible interventions), weight monitoring, swallowing and chewing activities, and oral care of the HNC patients. Similarly, the oncologist should offer an open and approachable relationship with other members of the team to ensure that necessary interventions will be introduced from the onset. The future management of cachexia will need to consider combining sufficient nutritional intake, physical exercise and inflammation reducing and protein synthesis increasing medical treatment.

In conclusion, increasing muscle volume and decreasing inflammation remain crucial components of cachexia management. However, feasible and partly novel approaches to enhance the effective management of HNC-induced cachexia warrant further studies. Additionally, cachexia assessment should be employed as a routine part of the management of HNC. Considering the adverse effects of this syndrome on the quality of health and chance of survival, it is important that a standard of care regarding the available interventions should be considered by the concerned authorities and organizations.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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