Received: 22 February 2023 | Accepted: 13 September 2023

DOI: 10.1111/odi.14749

ORAL DISEASES Leading in Oral, Maxillofacial, Head & Neck Medicine WILEY

REVIEW ARTICLE

Cachexia and head and neck squamous cell carcinoma: A scoping review

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Abstract

Objective: The objective of this paper was to provide an understanding of cachexia in relation to oral squamous cell carcinoma relevant to oral health care. The paper is a scoping review of aspects of the clinical presentation, aetiology and management of cachexia in relation to oral health and oral health care.

Methods: A combined search of MEDLINE and EMBASE databases (via OVID) was conducted using the terms ([Head and Neck] OR [Oral Squamous Cell Carcinoma]) AND (Cachexia). Duplicates were removed and results were subsequently limited to studies published between 2000 and 2023, humans and English language. After screening and full-text assessment a total number of 87 studies were included in the review.

Results: It is evident that cachexia is a not uncommon feature of patients with advanced malignancy of the head and neck driven by a multitude of mechanisms, induced by the tumour itself, that lead to reduced nutritional intake, increased metabolism and loss of adipose and skeletal tissue.

Conclusion: While a variety of nutritional, physical, psychological and pharmacological interventions may improve quality and duration of life, ultimately the diagnosis of cachexia in relation to head and neck cancer remains an indicator of poor life expectancy.

KEYWORDS
cachexia, head and neck neoplasms, squamous cell carcinoma of head and neck

1 | INTRODUCTION

Cachexia is defined as a complex multifactorial metabolic syndrome characterized by an unintentional weight loss with a progressive loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support leading to progressive functional impairment (Fearon et al., 2011). The term is derived from the Greek words κακός *kakos*, meaning 'bad things' and ἕξις *hexis*, meaning 'condition' or 'state of being' (Powrózek et al., 2021; Richey et al., 2007). Although most commonly associated with malignancy cachexia may arise with several chronic or end-stage diseases such as infections, severe HIV disease (e.g. Acquired Immune Deficiency Syndrome), congestive heart failure (CHF), chronic renal failure (CRF), rheumatoid arthritis (RA), tuberculosis (TB) and chronic obstructive pulmonary disease (COPD) among others (Mantovani & Madeddu, 2009).

About 50%–70% of patients with head and neck (HNC) cancer are diagnosed with malnutrition of varying extent of severity, and progressive loss of weight is frequently one of the early conspicuous signs of cancer (Andreoli et al., 2011). Approximately 40% of HNC patients have cancer cachexia at time of treatment (Jager-Wittenaar et al., 2017; Kwon et al., 2017). Cachexia can have a

significant impact on patients' quality of life (QoL) and is often associated with substantially increased mortality rates—20%–30% of cancer patients die of cachexia-related complications such as cardiac or respiratory failure (Couch et al., 2015a; Couch et al., 2015b).

The incidence and severity of cachexia in HNC patients seem to be strongly correlated to the site and stage of the tumour (Solís-Martínez et al., 2022), thus, perhaps unsurprisingly, such weight loss is more frequently seen with advanced-stage cancers of the oropharynx, hypopharynx and supraglottis (Jager-Wittenaar et al., 2007).

2 | METHODOLOGY

A combined MEDLINE and EMBASE (via OVID) search was undertaken using terms [(Head and Neck Cancer) OR (Squamous Cell Carcinoma of the Head and Neck) OR (Oral Cancer) OR (Oral Squamous Cell Carcinoma)] AND (Cachexia) (Figure 1). Duplications were removed and the search results were limited to studies published between 2000 and 2023, humans and English language. Inclusion criteria were observational studies, clinical trials, systematic reviews with or without metanalyses and comprehensive scoping reviews. Commentaries, editorials, letters to the editor, animal experiments and care reports were all excluded. Also, articles describing cachexia of other diseases were excluded.

3 | RESULTS

3.1 | Staging

Cancer cachexia is a continuum that consists of three stages of clinical significance: pre-cachexia, cachexia and refractory cachexia (Figure 1). However, not all patients will progress through all stages of this continuum as this depends on several factors such as the type and stage of the malignancy, the presence of systemic inflammation, decreased food intake and the degree of response to the anti-cancer therapy (Fearon et al., 2011; Figure 2).

The clinical significance of this classification is that it encourages early identification and intervention, ideally at the pre-cachexic stage, but definitely before the refractory stage (Couch et al., 2015a; Couch et al., 2015b).

3.2 | Pathophysiology

The physiopathology of cancer cachexia is not fully elucidated. There is an overall metabolic state characterized by increased energy expenditure, insulin resistance, lipolysis and proteolysis, leading to skeletal muscle atrophy (with or without loss of fat mass) (Matsuzuka et al., 2019; Powrózek et al., 2021). It seems that several tumour and/or host factors (e.g. hormones, cytokines) induce energy imbalance (increased energy expenditure rate), negative protein balance (increased proteolysis and decreased protein synthesis) and increased

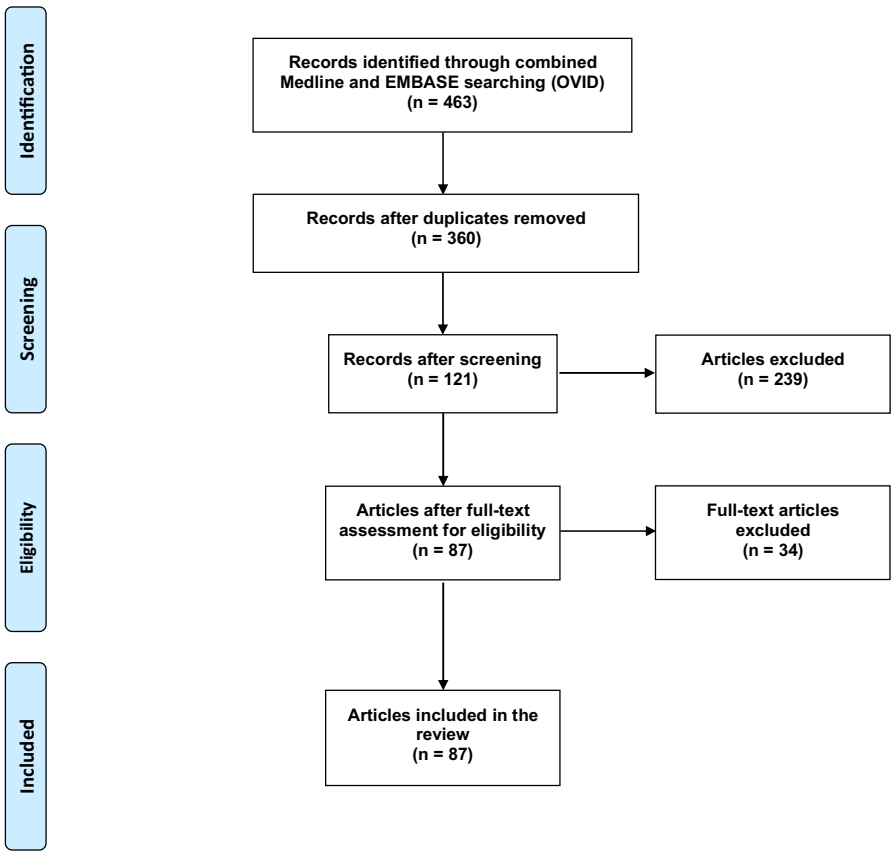

FIGURE 1 PRISMA flowchart showing the research strategy and results.

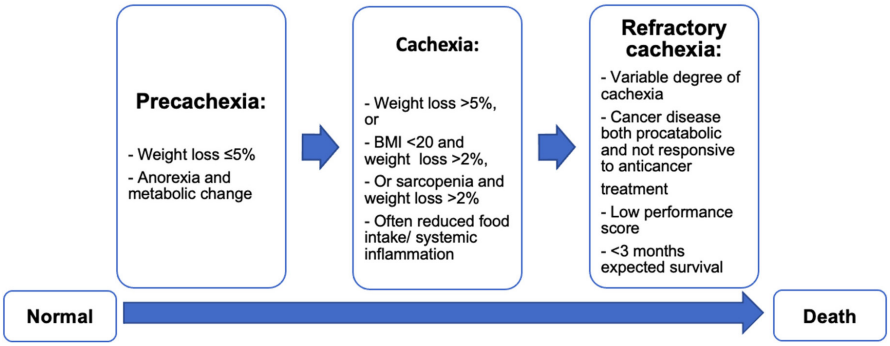

FIGURE 2 Stages of cancer cachexia (Fearon et al., 2011).

lipolysis resulting in anorexia, muscle atrophy and depletion of the adipose tissue thus promoting cancer cachexia (Mendes et al., 2015).

The precise physiopathology of cancer cachexia remains unclear, but factors such as energy imbalance, disproportion in hormones and cytokines secreted by the tumour and dysregulation of energy expenditure by the hypothalamus have all been proposed (Muthanandam & Muthu, 2021). It was originally believed that energy and substrate expenditure by tumour cells promote the development of cancer cachexia, but substantial cachexia often develops before tumour burden reaches 1% of body mass (Fearon et al., 2012), which makes it unlikely that metabolism is impaired solely by this mechanism.

3.2.1 | Anorexia and decreased food intake

The hypothalamus is the key region for the control of energy homeostasis in the body and is the CNS area where hundreds of signals converge, including hormones, nutrients and cytokines, to coordinate the complex energy consumption-food intake balance physiology (Blanco Martínez de Morentin et al., 2011; Pimentel et al., 2014). The hypothalamus consists of neurons that orchestrate the secretion of anorexigenic (i.e. reduces appetite) (cocaine- and amphetamine-regulated transcript (CART) and pro-opiomelanocortin (POMC)) or orexigenic (i.e. stimulates appetite) (agouti-related protein (AgRP) and neuropeptide Y (NPY)) neuropeptides to control food intake (Mendes et al., 2015).

There is some evidence that the melanocortin system—which is primarily composed of POMC neurons that secrete alpha melanocortin (aMSH) and exert their anorexigenic effects on neurons that contain the melanocortin 4 receptor (MC4R)—plays a key role in hypothalamus dysfunction (impaired oral intake) in cancer cachexia (Silva et al., 2014). In cancer cachexia, chronic inflammation induces the expression of pro-inflammatory cytokines (e.g. IL-1) in the hypothalamus, leading to inactivation of NPY/AgRP neurons and activation of POMC/CART neurons, resulting in various symptoms such as anorexia (Nishikawa et al., 2021). Therefore, peripheral hunger signals can reach the hypothalamus but are unable to induce a response because of the effects of such cytokines, thus promoting the cachectic process (Thomas, 2007). However, MC4R is also expressed in orexigenic neurons, which are inhibited by αMSH, thus decreasing NPY/AgRP release (Laviano et al., 2008). Therefore, it seems that hyperstimulation of POMC neurons occurs synergistically with the inhibition of NPY/AgRP causing disruption of melanocortin system which induces neuroendocrine-axis-mediated cancer cachexia (Mendes et al., 2015).

In addition to anorexia, cancer-associated decrease in dietary intake is also attributed to a variety of symptoms (i.e. nausea, vomiting, diarrhoea, constipation, dysgeusia, depression, anxiety, pain), collectively known as nutrition impact symptoms (NIS) (Kubrak et al., 2010).

Reduction in dietary intake in HNC patients is often further complicated by the site of tumour making such patients a distinctive nutritionally vulnerable group as a consequence of additional NIS such as dysphagia, mucositis, xerostomia, dental problems and difficulty in chewing, which are not only associated with the cancer itself but also with the subsequent treatment regimens, that is definitive radiotherapy (RT) alone or for more advanced cancers with RT in combination with surgery and/or chemotherapy (Couch et al., 2007; Vissink et al., 2003). But the evidence on the role of reduced dietary intake in cancer cachexia is inconsistent. Indeed, unresponsiveness to the correction of nutritional intake via conventional ways is a key feature of cachexia (Fearon et al., 2011). Even total parenteral nutrition failed to improve physical functioning, quality of life (QoL) or survival, and generated more serious adverse events, than oral feeding only among patients with advanced cancer cachexia and no intestinal impairment (Bouleuc et al., 2020).

3.2.2 | Increased metabolic rate (hypermetabolism)

Tumour cells are characterized by high glucose uptake which is utilized in an inefficient glycolytic with an overproduction of lactate, that is subsequently recycled into Cori's cycle (gluconeogenesis), thus further increasing ATP consumption, significantly increasing metabolic energy demand to skeletal muscles and fat tissues in weight-losing cancer patients. Such high rates of glycolysis could persist even with sufficient oxygen supply (Warburg effect; Fearon et al., 2012).

An alternative mechanism which perhaps contributes to the hypermetabolism in cancer cachexia is the overexpression of mitochondrial uncoupling proteins (UCPs) which play an essential role in shifting proton gradient between mitochondrial intermembrane space and matrix to produce heat instead of ATP (Fearon

et al., 2012). Indeed, UCPs have been found to be overexpressed in the skeletal muscle of patients with upper gastrointestinal cancer and weight loss, compared to counterparts with stable weight (Collins et al., 2002), and during switch from white adipose tissue (or WAT responsible for energy accumulation in intracellular lipid droplets) to brown fat (for energy dissipation), a phenomenon termed WAT browning, leading to increased lipid mobilization and energy expenditure which takes place in the early stages of cancer cachexia, before skeletal muscle atrophy (Petruzzelli et al., 2014).

3.2.3 | Skeletal muscle atrophy

Loss of skeletal muscle mass represents an essential feature of cachexia (Fearon et al., 2011), which often results in progressive functional impairment, poor quality of life (QoL) (Fearon et al., 2013) and may potentially increases the risk of respiratory failure which is a major cause of death in cancer patients (Houten & Reilley, 1980). Skeletal muscle wasting occurs largely as a result of imbalance between protein synthesis and degradation, particularly increased proteolysis (Schmidt et al., 2018). There are three proposed pathways to describe protein degradation in skeletal muscle: the ubiquitin–proteasome pathway (UPR) pathway, the autophagy pathway and calcium-activated protease calpains (Peixoto da Silva et al., 2020).

Cancer cachexia induces the transcription of key E3 ligases—such as the muscle atrophy F-box protein 1 (MAFbx), the muscle RING finger containing protein 1 (MuRF1) and Atrogin-1—(Acharyya et al., 2004; Penna et al., 2018; Porporato, 2016), which mediate the proteasomal degradation of structural muscle proteins—including myofibrillar components—by overactivation of the ubiquitin–proteasome pathway (UPP) (Cohen et al., 2015). Studies have also shown that members of the TGF-b family, namely myostatin and activin A, induced muscle loss through the activin receptor type IIB (ActRIIB), and that blockage of ActRIIB strongly offset cachexia and improved survival in cancer-bearing mice (Zhou et al., 2010). Finally, cytokines such as TNF-α and IL-1 and proteolysis-inducing factor (PIF) cause activation of forkhead box O (FOXO) family transcription factors, which increases muscle wasting (Argilés et al., 2014; Porporato, 2016).

There is now growing evidence that autophagy (i.e. cellular degradation of redundant components) upregulation plays a role in skeletal muscle wasting (Porporato, 2016). Indeed, a clinical study which compared oesophageal cancer patients with weight-stable non-cancerous controls identified autophagy as the main promoter of skeletal muscle proteolysis (Tardif et al., 2013). Another study which investigated a cohort of 92 patients with gastrointestinal cancer demonstrated increased expression of GABARAPL1 (an interactor of lysosomal vesicles and autophagy inducer) compared with healthy controls (Boyer-Guittaut et al., 2014).

Loss of myofibrillar proteins seems to play a potential role in muscle-wasting conditions. However, intact myofibrillar proteins are not degraded by the proteasome (Smith et al., 2011). Several mechanisms have been described the release of myofilaments from the sarcomere and the subsequent ubiquitination and proteasome-dependent degradation of the myofilaments (Hasselgren & Fischer, 2001; Jackman & Kandarian, 2004). One example for these mechanisms is calpain-dependent cleavage of myofilaments and proteins that anchor myofilaments to the Z disc (Goll et al., 2003). A case–control study which compared muscle calpain activity in 15 biopsy-proven gastric adenocarcinoma, who presented with no or only minimum weight loss, with controls was approximately 70% higher in the cancer patients than in the controls. Interestingly, no patient with stage I disease had increased calpain activity (Smith et al., 2011).

3.2.4 | Adipose tissue depletion

In addition to skeletal muscle atrophy, a significant proportion of weight loss in cancer patients is attributed to the depletion of adipose tissue (Baracos et al., 2018). Available evidence shows that the reduction in fat mass results primarily from lipolysis rather than from irreversible degeneration of fat cells (i.e. apoptosis) (Rydén & Arner, 2007; Zuijdgeest-van Leeuwen et al., 2000) and that the overall rise in whole-body lipolysis in cachexic patients is approximately 50% (Hall & Baracos, 2008).

3.2.5 | Inflammation

Several pro-inflammatory cytokines, such as tumour necrosis factor alpha (TNF-a), interleukin-1 (IL-1), interleukin-6 (IL-6) and interferon-gamma (IFN-c), have been suggested as key role players in the pathogenesis of cancer cachexia (Mantovani et al., 1998; Moldawer & Copeland, 1997). But it is still unclear whether such cytokines are produced primarily by the tumour or host inflammatory cells, as both pathways have been hypothesized to be the source of the acute-phase protein response (APPR) seen in cancer-induced cachexia (Donohoe et al., 2011).

Both acute-phase reaction and the innate immune system have been shown to play a potential role in several metabolic pathways involved in cancer cachexia (Hanahan & Weinberg, 2011).

The tumour necrosis factor alpha (TNFα), which is secreted primarily by activated macrophages, has been linked to the central regulation of anorexia in the hypothalamus, to adipose tissue atrophy and insulin resistance (Fearon et al., 2012), and to increased protein breakdown by the UPS in skeletal muscle (Argilés et al., 2014).

Interleukin 6 (IL-6) contributes to acute-phase protein synthesis and activation in the liver, and unlike TNFα, IL-6 has been consistently associated with cachexia and low survival rates in cancer patients (Narsale & Carson, 2014).

Elevation of the acute-phase proteins (e.g. C-reactive protein (CRP)) which are synthesized in the liver in response to inflammatory cytokines, is a common feature of cancer cachexia patients and are believed to increased amino acid demand from peripheral tissues, mainly skeletal muscle (Fearon et al., 2012). Indeed estimation of CRP levels may aid the diagnosis, classification and be an indicator of prognosis of cachexia (Martin et al, 2021).

3.3 | Diagnosis

Due to the intricate nature of cachexia and its complex pathophysiology, an expert consensus was developed in 2011 to specify diagnostic criteria for cancer cachexia (Fearon et al., 2011). Patients must meet at least one of these criteria to establish diagnosis of cancer cachexia:

1. Weight loss >5% over past 6 months (in the absence of simple starvation); or
2. Body Mass Index (BMI) <20 and any degree of weight loss >2%; or
3. Appendicular skeletal muscle index consistent with sarcopenia (males <7.26 kg/m.; females <5.45 kg/m.) and any degree of weight loss >2%.

Other diagnostic criteria have also been proposed (Evans et al., 2008; Martin, 2016) with the aim of better identification and management of cancer cachexia in clinical practice. However, regardless of which criteria are used, *unintentional* weight loss—either independently or in combination with one or more additional factors (such as anorexia, decreased dietary intake, muscle atrophy, decreased strength, fatigue and biochemical markers)—represents the basis for the diagnosis of cachexia (Baracos et al., 2018). Not only that *unintentional* weight loss is frequently the first detectable sign of cancer, but also it infers the degree of debilitation of the body's energy and protein reserves, which ultimately determines prognosis (Fearon et al., 2011).

The clinical significance of weight loss in cachexic patients was confirmed by a large prospective cohort study of more than 8000 cancer patients which demonstrated that the percentage of weight loss (%WL) and BMI were independently predictive of survival (Martin et al., 2015). Indeed, a gradient system combining the two parameters was developed in which lower BMI and loss of weight correlated to increased risk of mortality. But BMI and %WL cannot serve as a surrogate feature to detect patients with—or at increased risk of—cachexia, especially as they do not provide accurate appraisal of a key feature of cachexia: skeletal muscle atrophy. Furthermore, additional information is needed regarding decreased dietary intake and biological markers of metabolic imbalance, which provide clinically feasible means with increasingly specific and more precise results (Baracos et al., 2018).

3.4 | Cachexia in patients with head and neck squamous cell carcinoma

Although patients with Head and Neck squamous cell carcinoma (HMSCC) are particularly at significantly risk of malnutrition, the precise links between this group of cancers and cachexia are, perhaps, not as well investigated as might be (Jager-Wittenaar et al., 2017). It is assumed that HNC patients are more prone to cachexia due the involvement of structures directly associated with food intake which frequently results in compromised mastication and deglutition, thus compromising patients' nutritional condition (Mäkitie et al., 2022). The HNSCC, particularly SCC of oral cavity, is different to other cancers because the tumour itself—especially when it is large—might result in dysphagia, odynophagia and/or physically obstruct or restrict dietary intake (Muthanandam & Muthu, 2021), potentially contributing to cachexia. But large HNSCC could also contribute to the development of cachexia through the secretion of inflammatory and other cachexic mediators (Muthanandam & Muthu, 2021). However, it seems that the nutritional deterioration in HNSCC patients is multifactorial, because apart from tumour-specific factors, treatment-related side effects seem to play a significant role, including nausea, vomiting, dysgeusia, dysosmia, oropharyngeal dryness, painful mucositis, extraction of unhealthy teeth prior to radiotherapy and gastrointestinal changes due to prolonged use of opioids (Gorenc et al., 2015).

The precise prevalence of cachexia in head and neck cancer remains largely unknown. It has been reported that 20.2% ± 2.9% of HNC patients had a significant weight loss (i.e. unintentional weight loss of ≥5% of body weight in 1 month or ≥10% in 6 months) at the time of diagnosis, but the prevalence increased to 32.2% ± 4.9% immediately before commencement of cancer treatment—often 21 days later (Couch et al., 2015a; Couch et al., 2015b). It also seems that the prevalence and degree of weight loss vary according to the location of the tumour and its stage. Indeed, weight loss is substantially higher in stages III and IV HNC in comparison to stages I and II (Bruzgielewicz et al., 2009; Ravasco et al., 2003). Moreover, cachexia is more prevalent in patient with larger tumours or advanced HNSCC stage (Jones et al., 2022; Kwon et al., 2017; Richey et al., 2007; Solís-Martínez et al., 2022). The prevalence of significant weight loss was more than 30% at the time of diagnosis for oropharynx/oral cavity, nasopharynx, hypopharynx and supraglottic larynx, and decreased to approximately 20% for subglottic or transglottic laryngeal cancers, and to <10% in SCC of the glottis and other cancers of the head and neck, such as SCC of the salivary glands, nose/paranasal cavity, thyroid and skin (Jager-Wittenaar et al., 2007). Furthermore, severe weight loss increased from 3% of HNC patients receiving radiotherapy prior to the treatment to 44% at the end of the treatment (Langius et al., 2010), and the prevalence of malnutrition increased from 24% at the onset of RT to 88% at the end (Unsal et al., 2006). But the precise prevalence of confirmed cachexia cases seems to vary not only between studies but also according to the time of diagnosis (Table 1).

Cachexia serves as a prognostic indicator for HNSCC and is associated with high morbidity and mortality rates, and poor quality of life (QoL) (Gorenc et al., 2015; Jones et al., 2022), regardless of the cancer stage or treatment or therapy applied (Hayashi et al., 2021). Indeed, disease-free survival (DFS) (time in months from the completion of treatment to the detection of cancer recurrence or death of any cause) and overall survival (OS) (time in months from diagnosis to the day of last visit or death due to any cause) were substantially shorter in HNC patients with rather than without cachexia (Orell-Kotikangas et al., 2017). The incidence of post-operative complications (e.g. fistula, major wound dehiscence and infection) was significantly higher in cachexic patients who underwent resection and reconstruction, with patients more likely to experience longer

TABLE 1 Prevalence of confirmed cachexia in HNC patients.

Study	No. of patients	Prevalence		
		Before/at time of treatment	At the end of treatment	Later follow up
(Jager-Wittenaar et al., 2017)	26	12 (46%)		
(Kwon et al., 2017)	361	22 (6.1%)	148 (41%)	66 (18.4%) 6 months after treatment and 65 (18.7%) 12 months after treatment
(Jones et al., 2022)	252	135 (53.6%)		
(Solís-Martínez et al., 2022)	79	57 (72%)		
(Orell-Kotikangas et al., 2017)	65	20 (31%)		

ICU and hospital stay (Jones et al., 2022). The impact of cachexia on HNC patients extends to the different treatment motilities, with cachexic patients more likely to experience severe treatment adverse effect such as mucositis and dermatitis and markedly reduced tolerance to treatment, frequently resulting in treatment interruptions, compromising the efficacy of these modalities (Couch et al., 2015a; Couch et al., 2015b). Furthermore, post-mortem autopsy examinations have shown that cachexia was the main cause of death in 10% of the patients (Sesterhenn et al., 2012). Similarly significant adverse events such as anaemia, leukopenia and neutropenia were more frequent in HNC patients who received chemoradiotherapy (Hayashi et al., 2021).

3.5 | Management

In view of the challenging multifactorial nature of HNC cachexia, multimodal treatment approaches have increasingly been applied to target underlying factors involved in the aetiopathogenesis of cachexia.

3.5.1 | Nutritional interventions

Nutritional interventions in HNC patients with cachexia generally consist of nutritional counselling, which is based on personalized advice to patients and carers to improve the quantity and/or quality of dietary intake; nutritional support, using a variety of snacks and drinks to add certain nutritional element to patients' diet and nutritional supplements. They aim is to offset hypermetabolism and decreased nutritional intake in cachexic patients (Couch et al., 2015a; Couch et al., 2015b). Oral dietary intake is the most preferable route and should comprise a balanced combination of protein, energy, fibres, electrolytes, vitamins and minerals (Muthanandam & Muthu, 2021).

Sometimes, nutritional support can sometimes only be delivered via artificial routes (enteral or parenteral) when oral intake is severely restricted by the tumour (e.g. local invasion and spread), or in cases where the GIT function is severely compromised (Couch et al., 2015a; Couch et al., 2015b). Administering nutrition supply enterally is performed through either nasogastric tube (NAG) or percutaneous endoscopic gastronomy (PEG) (Mäkitie et al., 2022). It is indicated in patients with existing malnutrition with anticipated interruption of oral feeding for more than 7 days (Gorenc et al., 2015). Parental route (i.e. intravenous administration of nutrients) is recommended for patients with severe mucositis or radiation enteritis, or patients with insufficient food intake (< 60% of energy expenditure) which is anticipated to last more than 10 days, when nutritional support for any reason cannot be given through the enteral route (Bozzetti et al., 2009).

Although artificial nutritional interventions have been shown to improve nutritional status, QoL and survival in HNC patients who were incapable of maintaining adequate oral food intake, they failed to improve signs and symptoms associated with cachexia (Couch et al., 2015a; Couch et al., 2015b).

Oral intake of the food of a 'normal healthy' diet is the preferred way to provide daily nutritional needs, but oral nutritional supplements are frequently required to complement insufficient energy and protein intake in cancer patients, especially with severely compromised patients where nutritional supplements replace normal meals. Studies have demonstrated that oral nutritional supplementation with omega-3 fatty acids, micronutrients, and probiotics improved BW, lean body mass, serum protein concentrations in HNC patients with severe cachexia (de Luis et al., 2013; Yeh et al., 2013).

3.5.2 | Physical exercise

An increasing number of studies have demonstrated that physical exercise in cancer patients is safe and can counteract loss of muscle mass and strength and functional performance. Physical exercise therapy can enhance muscle protein synthesis and can potentially reduce the catabolic effects and the extent of inflammation which are often associated with cachexia (Mäkitie et al., 2022). A 12-week regime of progressive resistance training (PRT) for upper extremity in HNSCC patients with shoulder dysfunction after neck dissection (no radiotherapy) improved muscle strength and endurance and reduced shoulder pain and disability (McNeely et al., 2008). Moreover, lean body mass (LBM), and muscle strength and physiologic performance significantly increased with time in in RT-treated HNSCC patients who underwent

12-week PRT protocol (Lønbro et al., 2013). A general home-based programme of 30–60-min sessions of aerobic moderate-intensity exercise (50%–75% of estimated maximum heart rate) three times a week have been proposed for cancer patients with pre-cachexia and cachexia (Arends et al., 2017). However, physical exercise can sometimes be extremely burdensome, particularly in patients with severe cachexia, thus alternative exercise approaches such as neuromuscular stimulation (a self-applicable, battery-powered home device which produces a controlled contraction and relaxation of the underlying muscles) can be considered (Muthanandam & Muthu, 2021). However, there is insufficient evidence to support the effectiveness and safety of physical exercise in patients with cachexia (Grande et al., 2014).

3.5.3 | Pharmacotherapy

Several pharmacologic interventions have been used in the management of cachexia in HNC patients. Generally, pharmacologic agents can be classified into two main categories based on their therapeutic objective: (1) appetite stimulants, such as corticosteroids (dexamethasone), progestagens (medroxyprogesterone and megestrol acetate), orexigenic agents (dronabinol, cyproheptadine, metoclopramide, nandrolone and pentoxifylline), anabolic androgens and ghrelin analogues; (2) other agents such NSAID (celecoxib), anti-cytokine agents (e.g. thalidomide) and anti-oxidant agents (a-lipoic acid and N-acetyl cysteine) (Mäkitie et al., 2022; Muthanandam & Muthu, 2021). But there is insufficient evidence to support the administration of any pharmacologic agent to improve cancer cachexia outcomes (Roeland et al., 2020).

The complex multifactorial pathogenesis of cancer cachexia has led to the recommendation that its management should include a combination of multi-nutrient (use of multiple single nutrients as intervention), multitarget (targeting different mechanisms of metabolic pathway associated with cachexia) and multimodal (combining one or more methods of treatment) interventions. The multimodal approach often consists of multidisciplinary care; management of secondary consequences of cachexia, pharmacotherapy, nutritional counselling and support, physical exercise and social and psychological support (Arends et al., 2017; Muthanandam & Muthu, 2021; van de Worp et al., 2020).

4 | CONCLUSION

Cachexia is not uncommon in patients who present with existing head and neck squamous carcinoma (HNSC) and in view of the likelihood that not all such cancers can be eliminated, many patients with such cancer will develop or have a worsening of cachexia. Recognition of cachexia may aid the identification and/or progression of the underlying malignancy as well as ensure patients are provided with optimum physical and psychological support to prolong quality life.

AUTHOR CONTRIBUTIONS

S. R. Porter: Conceptualization; supervision; project administration; writing – review and editing; visualization. **A. Ukwas:** Writing – original draft; methodology; formal analysis; investigation; resources.

ACKNOWLEDGEMENTS

The authors are indebted to Professor Paddy Stone, Professor of Palliative and End of Life Care, Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London for his invaluable guidance in the preparation of this manuscript.

CONFLICT OF INTEREST STATEMENT

None.

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How to cite this article: Porter, S. R., & Ukwas, A. (2023). Cachexia and head and neck squamous cell carcinoma: A scoping review. *Oral Diseases*, *00*, 1–10. https://doi.org/10.1111/odi.14749