

Understanding Cachexia in Head and Neck Cancer

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ABSTRACT

One of the major comorbidities of cancer and cancer therapy is posing a global health problem in cancer cachexia. Cancer cachexia is now considered a multifactorial syndrome that presents with drastic loss of body weight, anorexia, asthenia, and anemia. Head and neck cancer (HNC) patients are at a greater risk for development and severity of cachexia syndrome as there is direct involvement of structures associated with nutritional

intake. Yet, the scientific evidence, approach, and management of cachexia in HNCs are yet to be largely explored. The article aims to succinctly review the concepts of cancer cachexia with relevance to HNCs and summarizes the current findings from recent research.

Key words: Cachexia, cancer, head and neck cancer, oral cancer

Introduction

Cancer, as such, is alarmingly growing as a global health problem, and oral cancer ranks sixth among the most common cancer in the world while it ranks third in the South Asian subcontinent.^[1,2] Although there are many advancements in conventional therapeutic approaches to oral cancer, many drawbacks still exist. For instance, the chemo- and radio-therapies targeted as cancer treatment approaches result in more significant toxicities and physical and psychological changes, all affecting the quality of life (QOL) of a patient.^[3] Weight loss is one of the most common findings in oral cancer patients undergoing therapy. The prevalence of malnourishment and weight loss in subjects with head and neck cancers (HNCs) varies between 3% and 88%.^[4,5]

The malnutrition status due to tumor itself or the therapy is described in two terms: anorexia and cachexia.

Anorexia is the involuntary loss of appetite or desire to eat that results in reduced caloric intake and often weight loss. Cancer cachexia is an energy-wasting syndrome indicated by weight loss and inflammation. Cancer cachexia is described as complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. There is yet another condition termed anorexia–cachexia syndrome, which is a complex syndrome which is often defined in terms of its primary or secondary causes. The main features of cachexia include loss of appetite, metabolic alterations, loss of adipose tissue, and skeletal muscle mass, leading to weight loss.

Although many definitions are proposed by various authors to define cancer cachexia, the simplest acceptable definition is: weight loss >5% over the previous 6 months, weight loss >2% in individuals with a body mass

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index (BMI) below 20 kg/m², or sarcopenia is described as cancer cachexia.^[6] Primary causes are related to metabolic and neuroendocrine changes directly associated with underlying disease and an ongoing inflammatory state. Secondary causes are aggravating factors (e.g., fatigue, pain, dyspnea, infection) that contribute to weight loss. Cachexia is now considered as a major contributor to morbidity and mortality, to impaired QOL, and to healthcare costs. Overall, cachexia accounts for 20% of all cancer-related deaths.^[7] In patients with advanced HNC, those with BMI of 25 or less survive 24.6 months on average when compared with 28.3 months for patients with BMI >25.^[8]

HNC is unique among these conditions in that the disease directly involves the aerodigestive tract, leading to dysfunction in deglutition secondary to both local tumor invasion and treatment toxicity.^[9,10] Patients with oral cancer have greater risk for involuntary weight loss which is estimated to exceed 10% of initial body weight.^[11] In cases with HNCs, especially cancers in the oral cavity, the tumor itself could limit the intake of food, and this dysphagia plays an important role in the development of cachexia. However, those with severe dysphagia are also found to continue to eat sufficiently, and in many cases, even mild dysphagia could drastically limit food intake.^[12] Jager-Wittenaar *et al.*, 2017 reported that in HNC patients, muscle mass depletion was an important factor differentiating between cachectic and noncachectic patients, rather than amount of reduction in food intake.^[13]

In HNC patients, not only difficulty in food intake and swallowing leads to cachexia, but also loss of appetite and changes in smell and taste play a crucial role in weight loss.^[14] Large tumors in the oral cavity contribute to dysphagia associated weight loss by physical obstruction and limiting food intake. Large tumors are also associated with increased production of molecular cachexia and inflammatory mediators, which enhance the incidence of cachexia. In HNC cases, increased nutritional risk and overt malnutrition have been reported.^[15]

Compared to other cancer cases, cachexia is still a relatively unexplored phenomenon in patients with oral cancer. The aim of this paper is to succinctly review the concepts of cancer cachexia with relevance to HNCs in particular and summarize the current knowledge and present findings from recent research. This article also highlights the role of oral examination as part of physical examination in subjects with HNC and the role of oncology nursing in the same.

Prevalence of Cancer Cachexia

An overall prevalence of 21.7% is reported with more frequency in cancers of the digestive tube (8.7%),

followed by lung cancer (4.3%).^[16] The prevalence as high as 50%–80% is reported in advanced cancer.^[17] 20%–60% of 1-year mortality rate due to cachexia is also reported in patient with all types of cancer in Europe. Mortality rates of patients with cachexia are reported to be 80% in cancer cases.^[18] Wallengren *et al.* observed a prevalence of 12%–85% in cancer patients under palliative care.^[19]

Jager-Wittenaar *et al.*, in their study on patients suffering from HNCs, suggested a high prevalence of cachexia (42%) in patients with newly diagnosed cases.^[13] They also observed that muscle mass depletion was significantly more frequent in cachectic patients (67%) than in noncachectic patients. Couch *et al.*, 2015 in a review of cancer cachexia in patients with HNC reported a prevalence of 20.2%–32.2%.^[20] Kwon *et al.*, 2016 reported the prevalence as 6.1% during the pretreatment period to 41% at the end of the initial therapy.^[21]

Although reports are available for the prevalence of cachexia in patients with HNCs in general, no report is available particularly for cancers of the oral cavity. This needs attention by the scientific community.

Pathogenesis

Cancer cachexia syndrome is unique that anorexia alone is not able to cause cachexia. This is one of the key features that distinguish cachexia from starvation. In cachexia, adipose tissue and skeletal muscle mass are wasted, while muscle mass is preserved during starvation.^[22] The physiopathology of cancer cachexia remains unclear, but can be attributed to energy imbalance, disproportion in hormones and cytokines secreted by the tumor and dysregulation of energy expenditure by the hypothalamus.

First, there is alteration in the intake of nutrition regulated by the neuroendocrine system that results in anorexia. The hypothalamus is the master center that controls energy homeostasis, integrating the energy expenditure–food intake balance.^[23–25] Particularly, dysfunction in the melanocortin system of hypothalamus has a key role in cancer cachexia. Studies have found that decreased activity of neuropeptide Y/agouti-related protein neurons and hyperstimulation of arcuate pro-opiomelanocortin (POMC) neuronal cells of the melanocortin system is critical for neuroendocrine-axis-mediated cancer cachexia.^[26–30]

Second, the molecular signals such as various inflammatory mediators have direct effect on cachexia. It is well established that proinflammatory cytokines released from tumors promote cancer progression and anorexia.^[31,32] This gain is linked to melanocortin system of the hypothalamus. The excess cytokines produced by the tumor cells induce the neuronal cells of hypothalamus to express POMC, which increases the central melanocortin system.^[33–35] The

proinflammatory mediators most commonly associated with cancer cachexia are interleukin (IL) 1 β and tumor necrosis factor (TNF) α .^[36]

Apart from these proinflammatory mediators, other molecules such as ghrelin and parathyroid hormone-related protein (PTHrP) have also been found to play a major role. Circulating levels of ghrelin have been found to be high in cachectic patients.^[37,38] This is due to decreased ghrelin signaling in the hypothalamus due to cachexia.^[39] Studies have also found that treatment with systemic ghrelin increased food consumption in cancer patients.^[40] The PTHrP produced by the tumor cells produces muscle wastage apart from decreasing the intake in food.^[41] PTHrP is also found to activate hypothalamic urocortins 2/3 via vagal afferent pathways that inhibit gastric emptying.^[42] Recent studies have also found that AMP-activated protein kinase is a key mediator in balance of food intake and energy expenditure.^[43,44] Activation of this molecule blunts cancer-induced reduction of food intake and also attenuates inflammation.^[45]

On analyzing inflammatory activity between HNC patients, with and without cachexia, no significant difference could be observed. Similar finding was reported by Stegel *et al.*, 2016.^[46] Ye *et al.*, 2011 reported that nerve growth factor (NGF) can link oral cancer progression, pain, and cachexia. They stated that NGF was highly elevated in human oral squamous cell carcinoma tumors. The study further demonstrated that NGF blockade decreased tumor proliferation, nociception, and weight loss by orchestrating proinflammatory cytokines.^[47] Inflammatory mediators such as IL-6 and C-reactive protein (CRP) were found to be higher in HNC with cachexia. This implies that cancer cachexia in HNCs is associated with acute-phase response.^[12] Similar response was observed in patients with melanoma, pancreatic cancer, or lung cancer.^[48] Reverse transcription-polymerase chain reaction study results on tumors of head and neck suggested that the tumor mass was the major direct source of IL-6 which was found to increase the incidence of cancer cachexia.^[10]

Third, the mechanisms that induce adipose tissue loss contribute a lot to cancer cachexia. Adipose tissue wastage is not caused by cancer cells directly but by rather molecules termed as lipid mobilizing factors.^[49] Recent research has found that zinc-alpha 2-glycoprotein (ZAG) is unregulated largely in cancer cachexia patients. ZAG induces lipid utilization and increased fat oxidation in brown adipose tissue.^[50,51] Furthermore, TNF- α induces lipolysis by inhibiting lipoprotein lipase and glucose transporter 4 activit, y thereby decreasing lipogenesis.^[52] TNF- α activates MAP kinase that activates JNK and results in inhibition of preadipocyte differentiation.^[53] In patients

with cachexia, TNF increases chemotaxis of monocytes to adipose tissue. The activated monocytes further produce more proinflammatory mediators such as IL-1, IL-6, and TNF, resulting in more inflammation.^[54] This continues as a vicious cycle.

Fourth, the molecular mechanism of skeletal muscle wasting is an important contributor to cancer cachexia. Skeletal muscle wasting is due to both reduced protein synthesis and increased protein degradation.^[55] Proteolysis-inducing factor (PIF) has been isolated, and high circulating levels of the same have been found in patients with cancer cachexia.^[56] The PIF promotes protein degradation by increasing mRNA levels of proteasome subunits. It also inhibits protein synthesis by activating RNA-dependent protein kinase.^[57,58] Myostatin and activins, members of transforming growth factor B family, are also found to increase muscle wasting in cancer patients.^[59] They also decrease protein synthesis by inhibition of Akt/mTOR pathway.^[60] PIF was evaluated in various cancer subjects with cancer cachexia, and increased mRNA expression for the same has been identified, while another study reported no difference in PIF expression for cachectic patients.^[61,62] In a study done exclusively in HNC patients, PIF mRNA was not expressed by any tumor tissues. The authors hypothesized that PIF is being expressed by nontumor tissue at a different site or that the human homolog of PIF does not exist in HNC.^[12]

Not just oral cancer, but subjects with precancer also exhibit some forms of anorexia. Subjects with oral submucous fibrosis (OSMF) exhibited significant signs of fatigue and anorexia. The early process of cachexia is believed to develop during progression of OSMF, and the reason could be attributed to areca nut chewing which is believed to reduce hunger.^[63] Sathe *et al.*, 2015 reported a significant association between Grade IV OSMF and anorexia.^[64] This could be due to 5-hydroxytryptamine-mediated effects on energy metabolism and appetite induced by the components in the areca nut.^[65]

Treatment as the Cause

Cancer cachexia is a result of inadequate dietary intake and alterations in nutrition metabolism associated with the tumor. Apart from this, the therapeutic modalities of cancer such as chemotherapy and radiotherapy can indirectly result in cancer cachexia. The treatment modalities exacerbate xerostomia, dysphagia, and dysgeusia, which in turn decreases the food intake.^[66]

In HNC patients undergoing radiotherapy, weight loss and cachexia were associated with the following factors: site of the tumor other than tumors of larynx, stage of the tumor (especially stage II), pretreatment weight, adverse

effects of therapy, dysphagia before therapy, and nutritional and dietary intake during therapy.^[67]

In subjects with squamous cell carcinoma of head and neck (SCCHN) undergoing radiotherapy, majority experience weight loss. Subjects exhibiting weight loss present with greater treatment-related morbidity. According to Langius *et al.*, 2013, critical weight loss and worse disease-specific survival were found to be significantly associated.^[68,69] Kubrak *et al.*, 2020 reported that patients with HNC have many reasons to become cachexic when compared to patients with other tumors. Involvement of structures devoted to food intake, tumor-dependent anorexia, and finally the local toxicity of the oncologic therapy in addition to the common metabolic derangements lead to cachexic the state.^[70] Yueh *et al.* reported a 1-year survival rate of 4%–60% in oral cancer patients with and without previous radiation therapy.^[71] Lacy *et al.* reported a 2-year survival rate of 15% versus 37% in patients undergoing radiation therapy with and without weight loss.^[72]

Radiation therapy results in xerostomia, mucositis, and fibrotic changes in pharyngeal constrictor muscles and ligaments of supraglottic larynx. This will result in general difficulties during mastication and swallowing. Hence, sparing of these structures during therapy is of maximal importance. This will preserve quality of swallowing process and nutritional status of the patient.^[73,74] Al-Mamgani *et al.* reported that 65% of patients with locally advanced oropharyngeal cancer had to be put on feeding tubes.^[75]

Possible treatment-related factors contributing to cancer cachexia in patients with HNC are loss of dentition, mechanical interferences in the digestive tract, ill-fitting dentures, odynophagia during surgery, nausea, mucositis, thrush, fatigue, etc., due to radiation therapy and vomiting, diarrhea, taste alterations, and abdominal cramping following chemotherapy.

Consequences

Weight loss, anorexia, and cachexia in cancer patients are associated with survival time period in most of cancer cases. In subjects with ovarian cancer, there was an observed 7% decrease in survival for every 5% weight loss.^[76] Studies have also reported that lowest rate of weight loss had a median survival of 30.2 versus 7.5 months in those with the highest rate of weight loss.^[77,78] The reason for low survival rate can be attributed to increased incidence of radiotherapeutic, chemotherapeutic, and surgical complications in subjects with cachexia. In patients with weight loss, chemotherapy doses were lower; they developed more frequent and more severe dose-limiting toxicity.^[79]

In subjects with HNC, especially in oral and oropharyngeal carcinomas, loss of more than 10% body weight had strong

impact on 1-year survival. In subjects with >10% weight loss, survival was poorest.^[80] The author also reported that patients with early and late stages of disease had different survival rates even when associated with weight loss. Brookes *et al.* reported that in cases with HNC, 2-year survival rate for patients without weight loss was 57.5% whereas for those with weight loss was 7.5%.^[81] Regueiro *et al.* in cases with primary oropharyngeal squamous cell carcinoma reported that disease-free survival was greatly influenced by weight loss in conjunction with tumor size and lymph node status.^[82] Yueh *et al.* also found that weight loss in patients with second primary tumors of the oral cavity was highly predictive for mortality.^[71]

The next important consequence of cancer cachexia is the overall QOL. Cachexia can cause generalized feel of weakness, extreme fatigue, and poor physical performance, all leading to lower self-rated QOL. This can lead to increased emotional distress, furthering lowering the QOL indices. Patients who continue to lose weight while receiving palliative chemotherapy have reduced global QOL and performance scores when compared to those whose weight loss stabilizes.^[83] Kasvis *et al.* reported that well-being is negatively affected by anorexia and anxiety in all cancer cachexia stages, with fatigue also being predictive of poor well-being.^[84] Wheelwright *et al.* in a systematic review assessing the health-related QOL (HRQOL) of cancer patients with cachexia reported that a negative relationship between HRQOL and weight loss was found.^[85]

In subjects with HNC undergoing therapy, it was observed that fatigue levels correlated with survival. Increase in baseline fatigue scores correlated with 17% decrease in survival.^[86] Another study reported that in HNC patients, worst QOL scores were observed in subjects with weight loss of >10%.^[87]

Diagnosis and Screening

Diagnosis of cachexia is often complex that it requires diligent clinical examination of the patient. The following clinical assessment is of utmost importance: unintentional weight loss exceeding 5% during 6 months, progressive decrease in muscle mass especially in biceps and quadriceps, decreased food intake as evident from food intake recall register, self-reported increased general fatigue, and most importantly decreased scores in QOL survey and Karnofsky Performance Scale. Biochemical parameters such as increase in serum CRP, hematocrit, albumin, and fibrinogen are also considered to be diagnostic of cachexia in HNC cases. Nutritional assessment parameters such as increased resting energy expenditure evaluated by indirect calorimetry and decrease in lean body mass indicated in dual-energy X-ray absorptiometry (DXA) are also considered to be more

diagnostically accurate, especially monitoring patients after initiation of treatment for cachexia.^[88]

General signs and symptoms such as current weight compared to pretreatment or last recorded weight, change in strength, mobility, presence of peripheral edema, ascites, changes in tone and mass of major skeletal muscles, changes in color, tone and integrity of skin and oral mucous membrane, signs of weakness, confusion, dizziness and symptoms of dehydration such as increased thirst, decreased urine output, dry mouth, and skin are easily observable. The patient themselves or the caretakers can be taught to observe and report these signs and symptoms which will pave way for early diagnosis of cachexia.

The QOL of patients with cancer cachexia can be assessed by various standardized, validated tools such as functional assessment of cancer therapy general scale and the anorexia-cachexia subscale. However, these questionnaires are most widely used in research settings. In clinical practice, the revised Edmonton Symptom Assessment System that assesses lack of appetite with a numeric rating scale is more practical.^[89,90]

Various nutrition screening tools such as Nutritional Risk Screening Tool 2002 (NRS-2002), Nutritional Risk Index (NRI), Patient-Generated Subjective Global Assessment (SGA), Mini Nutritional Assessment, and Malnutrition Universal Screening Tool (MUST) are used in screening for malnutrition. Even though there is no universal gold standard screening tool for assessment of nutritional status in patients with cachexia, Kyle *et al.*, 2006 reported that NRS-2002 had higher sensitivity and specificity than the MUST and NRI, compared to SGA. The author also reported a significant association between length of hospital stay and nutritional status and risk by SGA, NRS-2002, MUST, and NRI.^[91]

Assessment of body composition in cachexia patients can be done by the assessment of BMI or estimated weight loss, assessment of fat and muscle mass using DXA, bioelectrical impedance analysis, or computed tomography.^[92] Hydrodensitometry (underwater weighing) and air displacement plethysmography (Bod Pod) and magnetic resonance imaging are considered the alternative methods to assess gross body composition. BMI, though a simple and easy tool in diagnosis, was found to severely underestimate the level of cachexia in HNC cases, the magnitude of discrepancy being 3–4-fold.^[93-95] Computed tomography (CT) imaging is considered to be the most accurate as it differentiates adipose tissue, bone, organs, and muscle, including degree of fatty infiltration by Hounsfield units. According to Ryan *et al.*, 2016, body composition measurements by CT imaging in cancer patients, 50%–80%

of patients were reported to have low lean body mass, a correlate of malnutrition.^[96]

Management

Management of cancer cachexia comprises mainly nutritional counseling and nutritional support. For prevention of further deterioration in nutritional status, nutritional supplements also play an important role. Nutritional interventions such as weight monitoring and nutritional counseling have been shown to improve health outcomes in HNC patients by decreasing weight loss, improving QOL, and physical function.^[97] Supplementation of nutrition can be done through two routes: enteral nutrition (EN) and parenteral nutrition.^[98] Subjects on treatment for HNC and oral cancers usually are found to have a normal functioning gastrointestinal tract, but they face difficulties in oral intake as most of the structures involved in mastication and swallowing may be compromised. Such subjects are usually fed through enteral route.

Feeding tubes are the first choice in such cases where the patients have swallowing disorders. SCCHN patients on intense radio- or chemo-therapy, where severe mucositis is expected are also fed through feeding tubes.^[99] Stages III–IV SCCHN patients who were tube-fed were found to exhibit less mean weight loss.^[100,101] Percutaneous endoscopic gastrostomy (PEG) tube is also used to feed the subjects directly into the stomach across the abdominal wall. SCCHNC patients fed through PEG exhibited improvement in QOL and survival rate.^[102] Silander *et al.*, 2012 reported significant improvement in mean body weight and improved nutritional status in subjects undergoing radiation therapy for advanced SCCHNC. Nasogastric tube (NGT) is another method of feeding in subjects who have already developed oral and esophageal mucositis due to radiation therapy. In a study done by Corry *et al.*, 2008, to assess the effectiveness of PEG tubes and NGT in terms of nutritional outcomes in patients with SCCHNC, no conclusion could be made regarding the most optimal method for routine use.^[103] However, swallowing outcome is better during CRT when NGT is used, rather than PEG in subjects with HNC.^[104] Parenteral administration of nutrition is indicated in subjects with gastrointestinal insufficiency, where intake of food and absorption of nutrients become severely compromised. This type of feeding is also indicated and preferred for patients under palliative care.^[105]

Another aspect in the management of cachexia is pharmacological therapy. Glucocorticoids are most commonly used to manage cachexia; this group of drugs can increase appetite and food consumption and better control pain and nausea.^[106] Dexamethasone, a mineralocorticoid,

is also a potent drug to manage cachexia. However, it is limited for use in subjects with less life expectancy because of its side effects such as osteoporosis, proximal muscle weakness, immunosuppression, and delirium.^[107] Megestrol acetate is another drug used to induce appetite in cachexia patients. This synthetic hormone improves appetite but has a small effect on weight gain. Mantovani *et al.*, 1995 reported an improvement in appetite and QOL score and a decrease in serum levels of IL-1, IL-6, and TNF- α in male patients with HNC after treatment with megestrol acetate.^[108]

Another group of drugs called orexigenic agents has also been tried in the treatment of cachexia. This group includes drugs such as dronabinol, cyproheptadine, metoclopramide, nandrolone, and pentoxifylline. These drugs have anti-emetic properties and have found to increase appetite. However, strong evidence for the use of this group of drug is not available.^[109] Omega 3 polyunsaturated fatty acids have emerged as a promising drug in cachexia management. This is termed as nutritional pharmacomodulation. Omega 3 was found to inhibit production of the IL-6, PIF, and LMF. and they also block ubiquitin/proteasome-induced muscle proteolysis. Wigmore *et al.*, 1997 reported an improvement in lean body mass of HNC patients with cachexia after treatment with omega 3 supplements.^[110] Other interventions using nonsteroidal anti-inflammatory drugs (celecoxib), anticytokines (thalidomide), and antioxidant agents have been tried as part of multimodal approach and were found to improve body weight and appetite. As with any chronic condition, individualized and integrated multidisciplinary approach will provide the best outcomes.

Numerous guidelines are available for assessment, monitoring, and management of nutrition in HNC patients. Curtin *et al.*, 2020 in a systematic review analyzed seven guidelines for nutritional assessment and management and found three that were specific to HNC patients: National Comprehensive Cancer Network (NCCN), Cumulative Index of Nursing and Allied Health Literature, and National Institute for Health and Care Excellence (NICE). NCCN recommends referring to dietician with initiation of treatment, while NICE recommends screening of patients for malnutrition and then referring to dietician if they are found malnourished.^[111]

NCCN guideline suggests that patients with HNC are prone to weight loss, which can often be severe, as a result of treatment-related toxicity, disease, and health behaviors. They recommend that all patients on treatment should receive continuous monitoring of weight and nutritional evaluation before and after treatment to assess the need for interventions.^[112] NICE guideline suggests that oral nutrition

support to improve nutritional intake should be considered for people who can swallow safely. Overall nutrient intake of oral nutrition support offered should contain a balanced mixture of protein, energy, fiber, electrolytes, vitamins, and minerals. In subjects with risk of malnourishment, or inadequate and unsafe oral intake, presenting with malnourishment, enteral tube feeding should be considered. In case of subjects with nonfunctional, inaccessible, or perforated (leaking) gastrointestinal tract, parenteral feeding is indicated.

Current concepts in the treatment of cachexia include multinutrient (use of multiple single nutrients as intervention), multitarget (targeting different mechanisms of metabolic pathway that causes cachexia), and multimodal (intervention combining one or more methods of treatment) interventions.^[113] Multimodal therapy includes multidisciplinary care; management of secondary consequences of cachexia, pharmacotherapy, nutritional counseling, exercise and physical activity, and finally, social and psychological support.^[114]

All the interventions mentioned before, aim at increasing the appetite, energy, and protein intake and in decreasing the inflammation. However, to modulate the alterations in catabolic pathways and insulin sensitivity, recent researches recommend exercise as part of therapy for cancer cachexia.^[115] In general, it is considered that cachexic environment increases inflammation, induced anemia by decreasing hemoglobin which in turn increases muscle pain and weakness, and hypogonadism that reduces muscle mass and bone mineral density. Effects of exercise include enhancing muscle protein synthesis, attenuating the catabolic effects of cachexia, and modulating levels of inflammation.^[116] Exercise also triggers IL-6 production, which is found to increase insulin sensitivity and reduce the production of proinflammatory cytokines. Given that insulin resistance is associated with increased muscle protein degradation, improved insulin action after exercise may help inhibit muscle protein breakdown.^[117]

Data from studies have reported that patients with advanced disease benefit well from exercise program by improved functions and QOL.^[118] Grande *et al.* in a systematic review determined the effects of exercise, compared to usual care or no treatment, on lean body mass, the main biomarker of cachexia, in adults with cancer. They concluded that the evidence for effectiveness of exercise in cancer cachexia is still insufficient. Considering these findings, physical activity and exercise program can be considered as a potential nonpharmacological treatment in cachexia.^[119]

Therapeutic exercise and physical activity, though beneficial, is not always practical. It requires time,

effort, and high levels of motivation. Hence, alternative approaches to physical activity are explored in recent times. A recent development in this line is neuromuscular electrical stimulation (NEMS), which is considered an exercise alternative to strengthen muscles. This self-applicable home care device is a battery-powered stimulator unit with self-adhesive electrodes that produces a controlled contraction and relaxation of the underlying muscles. Maddocks *et al.*, 2009 reported that changes in muscle strength parameters were good in subjects who received NEMS. Moreover, patient acceptance was excellent for this technique.^[120]

Role of oncology nurses

Oncology nurses play a crucial role in risk assessment of cachexia before the onset of condition. In case of HNC, they must be aware of the fact that patients receiving concurrent chemotherapy and radiation therapy may develop severe stomatitis and dysgeusia that may lead to secondary cachexia. In such cases, routine assessment of patients' nutritional status, including weight loss and reporting of nutritional deficiencies, becomes the important role of oncology nurses.^[121,122]

Patients with HNC are a unique patient population and require extensive educational, interventional, and holistic care during and after treatment. Malnutrition and cachexia in HNC cases are expected to be of early onset and more severe. Unlike other cancers, HNCs are often associated with surgical removal of vital structures involved in speech, mastication, deglutition, and salivary production. Such functional changes during surgery can lead to dysphagia that impairs a patient's ability to intake food by mouth. In addition to this, the effects of radiation and chemotherapy often result in secondary difficulties such as severe mucositis, burning mouth syndrome, and dental caries, all of which limit the intake of food. In such cases, PEG is of choice to ensure adequate nutrition to prevent or treat cancer cachexia. It is imperative that the patient, the dietician, and the oncology nurses maintain an open line of communication and work together to meet nutritional needs.

In cases with PEG feeding tubes, close attention must be paid to administration of drugs. For example, extended release and sustained release medications in crushed form should not be administered together via PEG. Another care that has to be taken is the fluid amount during medication administrations. To avoid discomfort related to high volume fluid, medications should be given with adequate time intervals. Flushing medications with lukewarm water are recommended. Time of administration of medications should also coordinate with tube feeding, especially in case it has to be administered on empty stomach.^[123]

Apart from this, oncology nurses play an important role in the management and rehabilitation of dysphagia. Dysphagia is reported in 50%–80% of the HNC cases.^[124] Swallowing is a complicated process that needs coordination between more than 25 pairs of muscles in the oral cavity, pharynx, larynx, and esophagus. Rehabilitation therapy involves several types of swallowing exercises to increase motility and strength in the affected area.^[125] Swallowing exercises may include using specific swallowing maneuvers, changes in body posture and range of motion, as well as resistance exercises or techniques. Oncology nurse should contribute to improve patients' nutritional status, work collaboratively with other specialties to aid in swallow deficits.^[126] They should establish simple swallowing maneuvers as part of routine care regimen in HNC case, even before the start of radiation or chemotherapy to lessen the long-term adverse effects and to improve oral nutritional intake.^[127] Collaborating this regimen with dieticians ensures adequate, safe nutrition and will identify patients with clinically significant aspiration.

Patients with HNC, especially if operated on, skin and oral care will fall last in priority. However, oncology nurses should be aware of expected oral cavity changes and educate the patient for self-monitoring. Apart from being responsible for the oral care of the patient, they should also guide the patient in performing self-oral care eventually. In the process of oral care, when mouthwashes are used, alcohol-containing mouth rinses are to be avoided.^[128] Apart from this, prosthetic rehabilitation of structures that were resected during surgery is one of the important treatment aspects to improve nutritional intake. Oncology nurses should be knowledgeable about interventions within their scope of practice and make referrals when necessary to manage dysphagia and maintain the patient's QOL.

Oral health awareness and oral care are crucial aspects of oncology nursing practice. Abu Sharour, 2019 in a cross-sectional study reported oral mucositis management among oncology nurses need to be improved.^[129] Pai and Ongole determined the nurses' knowledge and education about oral care in cancer patients undergoing chemotherapy and radiation therapy and found that nurses had poor-to-average knowledge regarding oral care in cancer patients.^[130] The author also reported that nurses expressed that oral care in cancer patients was one of the most ignored aspects in oncology nursing.^[131] Oncology nurses should understand that they play a key role in identification of changes in oral cavity such as severe mucositis, dry mouth, burning mouth, and increase in caries so that timely referral to a skilled dentist is taken care of to prevent any long-lasting and permanent damage. Obtaining this care is missing most of the time but is very

important to prevent long-term complications related to oral care, mastication, swallowing, and nutritional intake. The oncology nurses should include examination of oral cavity as part of routine physical examination. We recommend the importance of inclusion of cancer patient-specific oral care in the curriculum which can enhance competency of the qualified nurses in cancer wards.

Limitations

This review has presented the available literature on cachexia related to HNCs. This being a narrative review did not attempt to analyze the evidence regarding various aspects of cachexia in HNC cases. Though data available on the same with regard to prevalence and pathogenesis seems to be adequate, studies or well-designed trials on treatment and management are still limited. Further probing of literature in terms of specific methods of diagnosis, monitoring, and management of cachexia in HNCs is required to guide the oncology nurses in rendering evidence-based care.

Conclusions

Cancer cachexia is one of the most debilitating consequences of the disease and treatment. Malnutrition and cachexia are common problems among patients with HNC and yet are understudied. Cachexia in HNC patients needs special attention, as the disease directly involves the aerodigestive tract, leading to dysfunction in mastication and deglutition. Hence, management of such patients should involve multimodal approach rather than focusing on just nutritional supplements. Literature evidence points out that oral examination and care are often neglected in cancer and cachexia care by nurses. Oncology nurses should understand the uniqueness of the HNC cases in terms of cachexia and possess the education and skills necessary to provide evidence-based care throughout the management of dysphagia, thereby improving their quality of life.

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Conflicts of interest

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