Review Article

Oral Equilibrium in Cachexia

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Received: May 12, 2021; Accepted: June 10, 2021; Published: August 27, 2021

ABSTRACT

Oral cancer, a part of head-and-neck cancer (HNC), is associated with a high risk of cancer-associated weight loss causing cachexia which is still an understudied illness. Cachexia is a host-phagocytic syndrome caused by the multiple factors, resulting in the severity of heterogenic fashion. For the current review, a bibliographic search was done in PubMed and other databases for the English articles published from the year 1980 to 2021. Recent studies have revealed that cachexia associated with 35%–60% of all the oral cancer patients is either due to the implication of the tumor or obstruction of food intake for which a strong need for nutritional assistance and hydration is desired. The health of cancer individuals undergoing chemotherapy or bone marrow transplant is negatively affected by poor oral health and reduced dentition status. The impact of a deficient oral condition is not clearly understood to date, possibly due to the limited number of studies and a lack of widely accepted clinical trials to prevent cachexia. The masticatory function of such patients is drastically affected thus contributing to the decreased nutritional status causing wasting of tissues. The aim of this article is to provide substantial evidence that poor oral hygiene with an altered dentition status negatively influences the energy balance of oral cancer patients who experience wasting.

Key words: Cachexia, dentition, mastication, oral hygiene, tooth loss

Introduction

A major cause for head-and-neck cancer (HNC) mortality is oral cancer which is estimated to increase rapidly with 657,000 new cases each year and more than 330,000 deaths being reported (WHO).[1] Poor oral hygiene and dental status are believed to be a risk factor of any HNC cachexia, especially oral cancer. There are very few epidemiologic details regarding the dental health and oral hygiene of these patients.[2] Following their treatment course, oral cancer patients often face complex oral health issues.[3] The management of oral cancer patients will require sound treatment planning before chemotherapy or radiation therapy (RT). Of these, RT can result in either reversible or irreversible adverse effects and long-lasting toxic consequences.[4] Cachexia, an old disease, has a modern research area that has only recently been thoroughly studied.[5] The negative effect of cachexia on functional prognosis has received more attention compared to its negative impact on survival prognosis.[6] However, no standard treatment has been established so far for patients of oral cancer with advanced stages of cachexia. This is true because cachexia is primarily seen as a functional condition with a macroscopically invisible primary cause.[7]

Despite mounting evidence that poor oral health is a risk factor for oral cancer, little is known about its impact on cachexia patients. To fill this knowledge gap, this review

Access this article online

Quick Response Code:

Website: www.apjon.org

DOI: 10.4103/apjon.apjon-2139

Cite this article as: Darwin D, Castelino RL, Babu GS, Asan MF, Sarkar AS, Shaktivel S. Oral Equilibrium in Cachexia. Asia Pac J Oncol Nurs 2021;8:519-26.

article is aimed to signalize the effect of poor oral hygiene and dentition as the main threat that causes wasting in patients with oral cancer.[8]

The oral cavity acts as a gateway for the process of food intake and digestion. Poor oral hygiene and reduced dentition status have a direct impact on the gastrointestinal flora and the latter indirectly reduces the nutritional status of the oral cancer cachexic patients.[9] The available data regarding cachexia in oral cancer patients are subjective with very little quantitative data in the existing literature.[10] A computerized search was done in PubMed and other search engines to identify the impact of dentition status and oral hygiene in cachexic patients. The merit of this review is that it provides a collective narration of scattered literature on the influence of poor oral hygiene and dentition on the cachectic conditions of patients with oral cancer. It also emphasizes on the management of the oral complications of such patients. The following oral findings may reflect the existence of a depleted nutritional status which ultimately leads to muscle loss in the cachexic patients.

Oral Signs in Cachexia Associated with Oral Cancer Patients

Oral pain is the most commonly seen complication in cachexia associated with oral cancer.[11] This is mainly attributed to the after-effects of cancer treatment such as RT. Pain caused as a result of RT-induced mucositis is mostly due to neuropathic sensitization and direct tissue damage. The duration and severity of pain are impacted by the RT plan.[6] Studies to potentially prevent RT-induced mucositis pain are carried out which suggests the use of photobiomodulation therapy.[12] In addition, pain can also be reduced by protecting the ulcerated tissue with the use of coating agents.[4]

Cytotoxic therapy in cachexia associated with oral cancer patients induces mucositis, which is dose-limiting toxicity. This condition seen in cachexic patients may be due to decreased salivary secretion and atrophy of the mucosal tissues.[13] The use of epidermal growth factors in targeted drug therapy causes painful mucositis both within and outside the radiation area.[14] Often, chronic sensitivity of the oral mucosa persists after active therapy and may even worsen in cachexic conditions. Palliative management of this condition may include the use of topical analgesics or anesthetics frequently, coating agents which lubricate the mucosa along with avoidance of spicy, acidic, or abrasive food items.[4]

Various oral mucosal infections can manifest at the time of ongoing cancer therapy, and its diagnosis often can be difficult due to other symptoms and signs in the oral cavity that overlap potentially. These infections also make it difficult for oral cancer cachexic patients as it shows its severity.[4] The commonly seen viral infections in such patients belong to the herpes family. However, reactivation of these viruses is not common in cachexic patients.[15] Care must be taken to confirm the presence of any viral infection by the histopathological examination of any vesicles or ulcerations present on the mucosal surfaces of the oral cavity. Systemic acyclovir or valacyclovir is prescribed in such cases of herpes.[4,16]

Any preexisting chronic periodontal or dental infection may progress to a local bacterial infection which becomes systemic in a cachexic patient who is often immunocompromised. These patients must be subjected to periodontal and dental evaluation before therapy.[15] Commencement of proper control measures is advised to annihilate symptomatic or active foci of infection. Initiation of empiric drug selection should be promoted in case of systemic antibiotics.[4]

Oral cancer cachexic patients are more prone to local fungal infections.[15] A prevalence rate of 7.5%, 39.1%, and 32.6% has been seen prior to, during the course of therapy, and following therapy, respectively. Many Candida species such as *Krusei, Tropicalis,* and *Dubliniensis* are seen affecting the oral cavity, but *Candida albicans* is the most common organism that causes varying clinical presentations ranging from erythematous to nodular appearances in addition to burning sensation and taste alteration.[4] Effective management includes topical antifungal preparation for topical therapy and systemic agents such as fluconazole.[15] To prevent increasing resistance to these azole antifungal agents, proper identification of the fungal species and a choice of the most effective medication are necessary.[4]

Periodontal disease (PD) is caused by a chronic oral bacterial infection that causes gum inflammation and leads to the progressive loss of periodontal tissues and the alveolar bone that supports the teeth.[17,18] The factors such as smoking, alcohol, alteration in diet including low consumption of vegetables and fruits greatly influence the periodontal status. Although no mechanisms have been established so far, PD leads to chronic systemic inflammation and high exposure to carcinogenic nitrosamines through diet or smoking.[19] Cancer patients with a low socioeconomic status and inadequate access to dental care are also at a higher risk of developing PDs that can lead to compromise in the nutritional status.[9] According to the observations of Ye *et al.*, it was found that PD can increase the risk of oral cancer by 2 fold.[20]

Subsequently, PD over a long period represents a complex process that involves loss of tooth and the supporting alveolar bone. Loss of tooth may also be associated with dental caries. It is an indicator of dental neglect which is

common in low socioeconomic status.[9] Often, tooth loss due to PD is regarded as the representative measure of any dysfunction of an individual's immunity.[8] Failure to clear any posttreatment PD suggests a deficiency in tumor surveillance and consequently causes the progression of cancer.[21] A cohort study conducted by Qian *et al*. in the year 2020 to assess the elemental risk factors of oral cancer mortality revealed the impact of alveolar bone loss and missing teeth significantly increasing the risk of death in aged oral cancer patients.[22] A study conducted by Martins *et al*. in 2020 assessed the total number of missing teeth in a population of malignant neoplasm of the oral cavity. A tooth loss index of 48.6% was evident in the study population consisting of 35 individuals.[22] The management of the alveolar bone loss caused by PD can occasionally be restored by grafting.[23]

Community functional oral flora dysbiosis is revealed in the various stages of oral cancer patients. Several studies assessed the changes in the structure and function of the oral microbiome of these patients including environmental, demographic, and clinical varieties.[1] The presence of oral pathogens is known to have a direct effect on oral and esophageal mucosa by producing carcinogenic products.[24] A study conducted by Bornigen in 2017 considering the alterations of oral flora during the stages of the disease revealed that specific genera present in the oral cavity were regularly depleted or enriched ultimately decreasing the potential of various metabolisms.[1] Gram-negative anaerobes that are known to cause worse endodontic and periodontal infections were shown to be abundant. The examples include-Dialister (enriched) and Scardovia (depleted).[25] This also caused the loss of community diversity due to the reduction of a large number of groups that are known to inhabit various environments around teeth such as enamel, sub-gingival crevices, and epithelial surfaces.[25] Overall, the levels of organisms such as *Corynebacterium*, *Prevotella*, *Actinomycetaceae*, *Streptococcaceae*, *Rothia*, *Flavobacteriales*, *Proteobacteria,* and *Fusobacteriales* were depleted resulting in a community primarily of *Lactobacillales*. Periodontitis was shown to be associated with increased levels of *Fusobacterium*, *Eikenella*, *Leptotrichiaceae, and Capnocytophaga*.[26] These pathogens dysregulated the various mechanisms of inflammation in the cells of oral cancer.[23] Further studies including the distinct molecular detail of oral microbiome in cachexic patients of oral cancer should be commenced along with various methods to improve the early detection and alleviation of oral cancer microbiome.[1]

In oral cancer patients, masticatory efficiency is a significant feature that determines posttreatment quality of life.[9] Ability to chew is compromised frequently in patients with cachexia. Often, oncological surgery eliminates tumors at the expense of functional anatomy. For example, following procedures such as mandibulectomy or glossectomy, patients face difficulty in vertical mobility and transportation of food, respectively.[23] Masticatory performance of a subject can be measured by mixing ability test (MAT) which makes use of a two-colored wax tablet. Participants are asked to chew these colored wax tablets till a minimum thickness of 2.0 mm is reached. The measurement of the intensity of these two colors is analyzed through photographs.[27] The normal mixing ability index ranges from 0 to 30; a lower index implying a better masticatory function. In addition to MAT, other tests such as maximum bite force and maximum mouth opening (MMO) can also be used to evaluate the masticatory performance of the patients.[23] In cachexic patients, the number of occluding pairs of premolars was found to be reduced, directly influencing their masticatory function.[28] Often, the status of the first permanent molar is regarded as "Cornerstone of dental occlusion, masticatory function, and jaw development."[29]

Trismus (restricted mouth opening) is mainly attributed to the invasion of the tumor, tumor-induced muscle spasm, RT-induced fibrosis, formation of edema after surgery or pain.[21] It is considered one of the late complications of the treatment of oral cancer.[22] It has a negative effect on the patient's quality of life as it influences their nutritional status.[30] A MMO of <35 mm is currently the most recognized criterion for diagnosing trismus. However, this criterion is complicated in partially dentate and edentulous patients.[31] In posttreatment patients, a debilitated oral mucosa along with pain and limited mouth opening suspends a proper oral hygiene. In addition, trismus is more commonly seen in completely edentulous patients which substantially decreases their ability of mastication.[21] Over the years, the survival rate of these patients has drastically reduced and may result in permanent sequelae of cachexia.[22]

Xerostomia is one of the most common complications which are seen posttreatment in the cachexia associated with oral cancer patients.[32] About 80% of patients usually report dryness of the mouth which is also an important risk factor for radiation caries (RC).[33] Usually, patients accommodate their symptoms and do not complain about dry mouth but if hyposalivation persists, the risk of oral infection increases.[34] The management includes the use of salivary substitutes which relieves the symptoms of dryness. Systemic sialogogues like pilocarpine which stimulates the production of saliva are also included.[33]

A secondary effect of radiation-induced xerostomia is the most commonly accepted etiology of breakdown of

dentition postradiation.[4] Several studies have established the correlations between dental caries and radiation.[33,35] However, it must also be noted that the dental lesions seen postradiation can vary from that of dental caries seen in nonirradiated patients in terms of development pattern, clinical appearance, and the progression of such carious lesions.[36] Proximal areas between teeth, pits, and fissures are the common sites for classic dental decay. On the other hand, dental caries that are seen postradiation are more common in cervical, incisal, and cuspal regions.[37] These are the areas of the mouth that are more prone to decay due to (incisal/cuspal) occlusal loading and subsequent flexure (cervical).[33] Such carious teeth are also reported to have a brownish-black surface discoloration which is different from nonirradiated carious teeth.[35] A cross-sectional study was done by Bhandari *et al*. in a population of 89 HNC patients who had undergone RT. The present study aimed to quantify the RC. Obtained results revealed the presence of a considerably high level of untreated dental caries which was up to 97%.[3] Several studies have highlighted the considerable decrease in the sensibility of pulp at the end of RT and no response was recorded to cold tests also. Electric pulp testing values increased at regular intervals after receiving RT.[36] Restoration of minimal to moderate dental caries and appropriate replacement restoration of any existing restoration with secondary dental caries should be encouraged.[35]

Osteoradionecrosis (ORN) is a known risk factor, particularly when RT involves the body of the mandible. Increased incidence may also be seen in patients on antiresorptive medications like denosumab or bisphosphonates and other immunosuppressive medications.[2] Primary approach for the management of ORN as given by an experienced health-care team is by the use of hyperbaric oxygen therapy. Recent literature studies have also highlighted the role of Vitamin E and pentoxifylline in the management of ORN.[4] A summary of the various oral signs seen in cancer cachexia caused by oral hygiene is listed in Table 1.

Cachexia Associated with Oral Cancer in Pediatric Patients

Although there is advancement in the early diagnosis and management leading to increased survival rates, the diagnosis of oral cancer is never welcomed in society, and it can be even more unexpected when it occurs in an infant or adolescent.[36] Several studies report the aggressive nature of oral cancer with poor prognosis in young adults as they are highly susceptible to the stomatotoxic effects of treatment like chemotherapy.[37] However, there has always been a missing section of literature on the cachexic condition of such oral cancer patients. After-effects of RT include microdontia, agenesis, hypoplasia and delayed development of dental structures with root shortening.[10] Persistent infection of periodontal tissues and dental pulp, oral mucosal ulcerations, lymphadenopathy, petechiae, taste dysfunction, and high prevalence of neglected dental caries significantly have a negative impact on the nutritional status of such cachexic patients ultimately increasing the risk of death.[38] Occasionally, the development of oral ulcerations was found to be associated with the administration of the drug-methotrexate.[36] Often, immunocompromised patients are prone to infections such as herpes simplex virus which follows an atypical course.[38] However, the occurrence of candidiasis and xerostomia as a result of aggressive chemotherapeutic regimens is shown to have a low incidence in pediatric cachexic patients.[36] Parents should encourage proper oral hygiene practices such as supervision of brushing using soft-bristled toothbrushes to prevent plaque accumulation, frequent replacement of toothbrushes as it may get colonized with oral bacteria and use of an alternate toothpaste in case of oral mucosal ulcerations.[37] In addition, periodic dental check-up, dietary advice, topical fluoride applications, management of dental caries, will help in establishing an adequate dentitional status required to improve the quality of life of cachexic patients.[38,39]

Nutritional Necessity

According to the European Society of Parenteral and Enteral Nutrition guidelines: Nutritional intervention in cancer patients aims in diagnosing, preventing as well as treating malnutrition through nutritional counseling either with or without oral nutritional supplements, or artificial nutrition like parenteral or enteral nutrition that affects the recovery and survival of the patients.[29] A brief description of the necessary nutritional intake of oral cancer patients associated with cachexia is given in Table 2.[40] Energy can be measured by total energy expenditure or by estimation of resting energy expenditure and multiplying it by the level of physical activity.[40] Energy expenditure in cancer can be affected by the composition of the body, systemic inflammation, tumor burden, activation of brown adipose tissue, various treatment modalities, physical activities, and diet.[41]

Importance of Oral Care in Cancer Cachexia

In cachexia associated with cancer, the management of the oral signs and symptoms along with nutritional supplementation can stabilize the body weight.[42,43] Malnutrition in such patients may also be attributed to the

Table 1: Summary of the oral signs in cancer cachexia caused by oral hygiene

Oral signs	Cause
Pain	Due to after-effects of cancer treatment with its severity impacted by the treatment
Oral mucositis	Seen due to decreased salivary secretion and atrophy of the oral mucosa
Viral infections	These are most commonly caused by the viruses that belong to the herpes family
Bacterial infections	Any prior tooth infection or chronic periodontal conditions leads to a local bacterial infection
Fungal infections	Burning sensation, dysgeusia, and a variety of other clinical presentations are seen in the oral cavity which is most commonly caused by *Candida albicans*
Periodontal disease	A chronic bacterial infection causes periodontal diseases. Nevertheless, it is also heavily influenced by a number of other risk factors in the cachexia associated with oral cancer patients
Alveolar bone and tooth loss	Alveolar bone loss is caused by persistent infections of the periodontium. Long-standing carious lesions may be related with loss of tooth
Dysbiosis of oral flora	Altered oral flora is known to be the causative agents of endodontic and periodontal infections. In addition, they also alter the regulation of inflammatory mechanisms of oral cancer
Masticatory efficiency	It is often compromised as a result of oncological surgery performed at the expense of functional anatomy. Often, the number of occluding posterior teeth is found to be reduced in the oral cancer patients associated with cachexia
Trismus	It is primarily seen as a complication of the treatment of oral cancer and affects the nutritional status of the patients
Xerostomia	It is the most important risk factor for carious lesions due to radiation therapy
Radiation caries	It is characterized by a brownish-black discoloration of the cervical, cuspal, and incisal region of the tooth structure
Osteoradionecrosis	It is also seen as a complication of radiation therapy which often involves the mandible

Table 2: Essential nutritional intake of cachexic patients according to the European Society of Parenteral and Enteral Nutrition guidelines[40]

The current recommendation of nutritional intake	Description
Protein	Protein intake to prevent low muscle mass in cancer 1.0-1.5 g/kg/day
Branched-chain AA	These have a significant role in the promotion of protein synthesis and amelioration of muscle mass in cancer
Beta-HMB	It is a potential preventative supplement, known to reduce the degradation of protein thus modulating the protein turnover Recommended supplementation: 3 g of HMB with 14 g of glutamine and arginine each
Glutamine	Acts as a nutrient for metabolism of muscle protein Acts as a source of energy for enterocytes in the gastrointestinal tract Recommended supplementation: 0.3 g/kg/day
Carnitine	Known to enhance the work performing moiety of the body tissues Lower levels are seen due to reduced food intake and increased excretion of urine in cachexic patients
Creatine	Known to improve lean mass and function of muscle and improves intensity bouts of activity
Eicosapentaenoic acid and fish oil	Being an anti-inflammatory substance, it enhances the performance status by increasing weight gain Recommended supplementation: 2.2 g/day
Vitamins and minerals	Essential: A, B, C, D, E, selenium and zinc of which Vitamin A and E are depleted due to RT Vitamin D improves muscle mass and function either with or without exercise Recommended Supplementation: 600-800 IU of Vitamin D combined with whey protein
Intake of fluid	Normal fluid status maintains blood pressure and perfusion Recommended supplementation: 3.7 L/day (males), 2.7 L/day (females)

HMB: Hydroxy Beta-methyl butyrate, AA: Aminoacids, RT: Radiation therapy

poor oral hygiene that is characterized by dental caries, tooth loss, alveolar bone loss, and associated consequences.[2,4] According to Kubrak *et al.*, cancer therapy patients with reduced masticatory function were at a high risk of muscle loss.[44] In case of oral infections, tube feeding with parenteral nutrition can prevent malnutrition.[45] Taste abnormalities may be corrected by increasing salivation using sialagogues and by oral zinc supplements such as zinc gluconate.[4,46] Care should be taken that root canal therapy or surgical extraction of tooth before RT does not result in serious consequence such as ORN, post-RT.[36] The use of topical fluorides (1% neutral sodium fluoride) for 1–2 min/day with the help of custom trays can prevent moderate/severe tooth damage. The oral hygiene status of the remaining dentition can be maintained by brushing twice a day along with the use of interdental techniques.[35] Early interventions with massage and range-of-motion exercises for the jaw will help overcome trismus and avoid extreme restriction of mouth opening.[4] Planning of dental care management should also include socioeconomic status, emotional state, and future quality of life of the cachexic patients into consideration. Oral nutrients and appetite stimulants help in satisfying the increased need for calories and proteins required to overcome muscle loss.[43] Further addressing the weight loss can also improve

the physical activity of such patients. The most beneficial and cost-effective method for the nutritional well-being of cachexic patients is individualized therapy.[40] The clinical guidelines produced by the Royal College of Surgeons of England in 2018 suggested including an early pretreatment oral assessment in all oncology protocols. An oncology team should include a qualified specialist who is responsible for the patient's oral care. The guidelines further state that the oncology patient discharge procedure should incorporate certain procedures to ensure continuing oral care.[47]

Cachexia associated with oral cancer is a continuum with 3 stages - precachexia, cachexia, and refractory cachexia. The changes in the appearance of face, impaired speech clarity, eating disorders, and dysphagia are some of the nutrition-impact conditions seen in oral cancer cachexic patients.[23] Merely, the assessment of weight loss and its reversal by conventional nourishment alone cannot appreciate the multi-dimensional syndrome of cachexia associated with oral cancer.[48]

A study conducted by Maier *et al*. in a group of 100 oral cancer patients with signs of cachexia revealed that there was a significantly increased incidence of grossly decayed teeth and tartar of more than 3 mm observed in 40.9% of the patients. The study concluded that the significantly worse oral hygiene and dental status in such patients may be attributed to many factors such as reduced salivary secretion, lower social strata often neglecting the dental check-ups, and seldom brushing habits due to tumor pain.[2]

The goals of the protocol of dental management should include a definitive treatment of any acute or chronic odontogenic infections including dental carious lesions and PD. Such an aggressive approach is necessary since these infections may progress into a systemic infection in the immunocompromised cachexic patients.[37] Any active source of infection in the oral cavity should be removed along with definitive treatment of any teeth with a questionable or a poor prognosis. Possible local irritants like rough areas of a restoration or a sharp tooth cusp must be removed. Patient education regarding the long-term effects of oral cancer treatment and the need for maintaining good oral hygiene must be emphasized.[25,36]

This article establishes the following possible interpretations:

1. Good oral health with periodic dental check-ups sustains as a marker of overall welfare
2. Poor oral hygiene with reduced dentition status has a direct effect on the progression of cancer into cachexic conditions due to the low nutritional status and associated reduced host immune response
3. Markers of oral health such as frequency of tooth brushing, usage of dental floss, annual dental visits, tooth loss, preserving a good oral bacterial flora to prevent dysbiosis, local mechanisms known to promote bacterial carcinogenesis which influences tumor behavior, and its advancement; these may serve as a proxy for oral health stressors that have the potential to influence mortality.[8]

Lack of routine oral hygiene practices can increase the progression of oral, esophageal, gastric, and pancreatic cancer by more than two fold.[9,49] In such cases, oral rehabilitation enhances the masticatory function of these patients.[28] In spite of ample time and investment into this field of research, there are no standardized guidelines for assessing, classifying, or treating the oral cancer cachexic patients.[48]

Conclusions

Lack of awareness and ignorance of the patients about the oral complications of cancer therapy may also direct effect deteriorating their nutritional status. Nurses being the patient's primary caregiver and their first point of contact can play an important role in detecting oral complications of patients undergoing cancer therapy. Adequate awareness about the oral signs and symptoms of cancer therapy among the nurses for a better nurse-assisted patient navigation can have a positive impact on the quality of life of the patients. Dental management of such patients is essential to decrease their symptoms and functional deterioration. The integration of oral physicians in the oncology team can aid in preventing, diagnosing, and treating the oral complications thus enhancing the quality of life of patients associated with cancer cachexia.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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