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Review Article

Nutritional Supportive Care in Head and Neck Cancer Patients – A Narrative Review

Doppalapudi Radhika[1], Arvind Muthukrishnan[1], Rakhi Issrani[2,3*]

[1]*Department of Oral Medicine and Radiology, Saveetha Dental college and hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, Tamilnadu, India.*
[2]*Department of Preventive Dentistry, College of Dentistry, Jouf University, Sakaka, Kingdom of Saudi Arabia.*
[3]*Department of Research Analytics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India.*

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Abstract

Head and neck cancer patients are more at high risk for malnutrition before, during, and after the cancer treatment procedures due to the proximity of key anatomical structures that are essential for mastication and deglutition. A multidisciplinary approach beginning with preliminary nutritional screening, comprehensive assessment, and nutritional supportive care is mandatory for all head and neck cancer patients. Such interventions not only improve quality of life but also increase the survival rate of the head and neck cancer patients. This updated narrative review focused on the recent updates of the various steps involved in the nutritional management of head and neck cancer patients, like pre-treatment nutritional care, screening and assessment, and nutritional interventions during and after cancer therapy with updates on nanoformulations of nutraceuticals. We reviewed all published literature between 2014 and 2024 about nutrition in head and neck cancer patients from major databases such as Embase, Web of Science, and PubMed. In addition to the nutritional parameters that should be considered during the nutritional assessment of patients with head and neck cancer, this review underscores the therapeutic efficacy of nutraceuticals in treating this disease. This narrative review added a note on recent updates on the use of a combination of novel nanoformulated nutraceuticals with chemotherapeutic agents, which were known for the improved drug delivery, such as targeting the neoplastic cells and thus preventing adverse effects.

1. INTRODUCTION

An estimated 325,000 people die from head and neck cancer each year, making it the fifth most prevalent cancer worldwide. The International Classification of Diseases (ICD-10), developed by the World Health Organization, classifies head and neck malignancies according to their anatomical location. Head and neck cancers are those that typically affect the mucosal surfaces of the salivary glands,

* Corresponding Author:
Rakhi Issrani
Affiliation 1: Department of Preventive Dentistry, College of Dentistry, Jouf University, Sakaka, Kingdom of Saudi Arabia.
Affiliation 2: Department of Research Analytics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India.
E-mail: **dr.rakhi.issrani@jodent.org; dr.rakhi.issrani00@gmail.com**

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nasal cavity, paranasal sinuses, pharynx, larynx, and oral cavity (1,2). The most prevalent cancer in the head and neck area is squamous cell carcinoma. The etiological factors include tobacco, smokeless tobacco products, alcohol use, HPV and EBV, occupational and radiation exposures, genetic disorders, etc. HPV-16 was identified as the causative factor in about 72% of the oropharyngeal cancer patients (2). Deficiency of vital nutrients, including vitamins, minerals, and antioxidants, causes nutritional deterioration, which impairs the body's immune system and its capacity to repair damaged cells, ultimately contributing to the progression of malignancy. It was discovered that in many cancer patients, malnutrition was caused by dietary attitudes and beliefs on particular food restrictions (3). Patients with head and neck malignancies frequently have poor nutrition, which is linked to immune function abnormalities that hinder the host's ability to fight off the cancer. Patients are at high risk for postoperative infections and problems due to immunosuppression brought on by tumors and malnutrition (4). Reduced food intake, loss of muscle mass with or without adipose tissue loss, and an imbalance in metabolic regulation are the hallmarks of cachexia, a poor physical state with progressive dysfunction. Metabolic alterations and treatment-related toxicity may cause loss of appetite and decreased nutritional intake, affecting the health-related quality of life and further hindering the survival rates of these patients (5).

Cancer cachexia is a complex metabolic syndrome characterized by multifactorial in origin with systemic inflammation, associated with loss of skeletal muscle mass, with or without loss of adipose tissue. Pré-cachexia, cachexia, and refractory cachexia are the three stages of cancer cachexia (5). Early nutritional intervention is provided to patients with pre-cachexia in order to prevent progression of malnutrition. Refractory cachexia is cachexia with increased catabolism and resistance to anticancer therapy (6). Higher intake of fruits and vegetables has been reported to lower the risk of oral cancer. High-energy, high-protein diets with oral nutritional supplements were the first recommendations for patients with head and neck malignancies. Nutritional therapy, exercise, and psychological counselling were found to be feasible in patients with cancer cachexia along with medicinal therapy (5,6,7).

The cellular disproportion between the supply of nutrients and energy and the requirements of the body for them to ensure growth and development, maintenance, and to perform specific functions is termed as malnutrition. The imbalance with inadequate intake leads to underweight, and excess intake leads to obesity and overweight (8). Malnutrition diagnosis can be confirmed by the presence of any two of these conditions like inadequate energy requirements, more than 5% loss of weight within 3 months, loss of subcutaneous fat mass, loss of skeletal muscle mass, reduction in grip strength and generalized edema (9). As per the recommendations of the European Society for Clinical Nutrition and Metabolism, the four reliable nutritional screening tools are the Malnutrition Universal Screening Tool, the Malnutrition Screening Tool, Nutritional Risk Screening, and the Mini Nutrition Assessment for identifying malnutrition risk score in the patients. Malnutrition significantly decreases the host response to cancer treatment, alters immune response, increases the risk of adverse effects of cancer therapy, and also leads to compromised health-related quality of life (10). Patients with head and neck malignancies are more susceptible to malnutrition, especially protein malnutrition, impaired antibody production, and immunosuppression. The etiological factors for nutritional deficiencies in these patients include poor dietary intake, surgical resection involving the tumour affecting the function of swallowing, and acute and long-term adverse effects of the treatment (11). The mode of the treatment rendered to the patients with head and neck cancer, such as surgery, radiotherapy, chemotherapy, or combination therapy, targeted therapy, and immunotherapy, may further compromise the nutritional status of the cancer patients. Immediate nutritional interventions are mandatory for patients that lose greater than 5% of total body weight within one month or more than 10% of total body weight within the six months of initiation of the treatment. The main nutrition goal of nutritional intervention in cancer patients is to maximize the nutritional intake or nutritional support therapy, thereby limiting the weight loss and improving patient survival rate (12).

The National Health and Medical Research Council has described few recommendations and adherence criteria for nutritional screening and assessment, quality of nutritional care delivered to patients, and monitoring and evaluation of nutrition for the cancer patients (13).

A) Pretreatment Nutritional Care Screening and Assessment

Each patient's individual needs are to be taken into consideration for achieving proper nutritional care. Individual nutrition counselling would be the first line of nutrition therapy and has a greater positive impact on patients during and after the radiotherapy treatment.

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Dietitians are qualified health care professionals who provide information on food and nutrition and deliver dietary advice to the patients. During nutrition counselling, the repetitive interaction and communication between the patient and the dietician provide the accurate need of the insufficient nutrients and changes in the daily eating habits (14). The symptoms that have an impact on nutritional intake, such as anorexia, oral mucositis, oral ulcers, and dysphagia, are the important predictors for reduced food intake through the oral route and weight loss in patients with head and neck malignancies before the treatment (15). The nutritionist/dietitian should conduct a baseline nutritional assessment for the patient before the treatment and provide proper nutritional counselling based on the food habits of the patient. The nutritional support is mandatory for the patients when BMI is less than 18.5 kg/m^2 and more than 10% of weight loss in overall body weight occurs within a period of 3 to 6 months and impaired or minimal oral intake of food occurs for more than 5 days. Nutritional support improves quality of life and prevents the effects of tumour therapies, thereby preventing malnutrition. The three important methods of nutritional support include oral, enteral, and parenteral routes (15). Oral includes traditional food fortification. Enteral nutrition is provided to the patients using tube feeding, either by nasogastric tube or percutaneous gastrotomy, in head and neck malignancies that are obstructing the swallowing function. National Institute for Health recommends less than 4 weeks for feeding through the tubes and Gastrostomy is recommended as a replacement to tube feeding for patients who require enteral feeding for more than four weeks. Parenteral nutrition is rarely used in head & neck cancers (16). The term prophylactic nutritional support was introduced over the last decade to avoid the interruption in the radiotherapy or chemoradiotherapy treatments. The feeding given to the patient through a nasogastric tube or percutaneous gastrotomy before initiating the treatment is termed prophylactic feeding. For the patients who are on nutritional supplements and unable to meet the complete nutritional requirements, enteral feeding using an nasogastric tube or percutaneous gastrotomy will be started, which is termed as 'reactive feeding.' The provision of enteral support is recommended when the oral intake declines below 50% from the baseline (17).

Nutritional assessment parameters

A. Energy requirements – 30 to 35 kcal/kg/day and it varies depending on the activity,

B. Protein requirements – 0.8 to 2 gm/kg/day and it varies based on therapy complications, and

C. Fluid requirements – 30-35ml/kg/day and it varies if there is excessive fluid loss.

B) Nutritional Care during Cancer Therapy and Monitoring

It is a common practice that the duration and dosage of the radiotherapy treatment is divided into doses over a period of 7 weeks for the Head and Neck cancer patients. This is a critical period for the rapid changes in symptoms of nutrition impairment and to initiate dietary advice. The impact of poor nutrition had significant adverse effect on the overall prognosis of cancer therapy, reducing patient survival and impaired quality of life in head and neck cancer patients receiving radiotherapy (18). During radiotherapy or chemoradiotherapy, 55% of the patients may lose around 10% of their body weight. For all the patients receiving concurrent chemoradiotherapy weight loss began after one week of initiation of the treatment. Clinical nutritional therapy with rigorous monitoring is advised in these patients while receiving the cancer treatment (19). The main goal of nutrition counselling is communication with the patients regarding their nutritional demands and continuous monitoring of the nutritional assessment and intervention are required at this stage. A multidisciplinary team involving medical teams with surgical oncologist and radiotherapist, nutritionists/dietitians, speech pathologist and language therapist, clinical nurses are necessary for monitoring the nutritional support (20). The clinician should identify the patients with malnutrition and early oral nutritional intervention and immunonutrition be provided immediately. Specific nutritional components are combined with whole protein, triglycerides, electrolytes and vitamins which are intended to enhance the immune function. Nutritional formulas with basic nutrients such as few amino acids like Glutamine and Arginine, Nucleotides (RNA) and lipids (omega-3 fatty acids) are known as immunonutrition. Arginine stimulates the function of lymphocytes and enhances wound healing. The Omega-3 fatty acids reduce proinflammatory mediators. An appropriate measured volume of the immunonutrition usually in the liquid form was found to be beneficial in providing the complete nutritional requirements of the patients (21). The nutritionist should monitor the patients before and after the treatment, individualized nutritional counselling be provided and modification of the diet according to their individual needs are to be implemented. The clinical nurses should make sure of the strict

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adherence of the patient to the diet (20). Individualized multimodal care is essential while initiating nutrition therapy with follow up visits and adaptation of diet pattern by patients aiming for further improvements (22).

C. Post Treatment Nutritional Care and Rehabilitation

For head and neck surgery, the Enhanced Recovery after Surgery recommendations advise patient mobilization within 24 hours to reduce overall post operative complications and hospital stay duration (23). Postoperative nutritional plans are to be developed by the experienced dietitian for these cancer patients (24). Dietitian determines the caloric and protein requirements, feeding schedules. Fluid and electrolyte imbalances may cause the risk of refeeding syndrome in these cancer patients. The risk factors of refeeding syndrome also include unintentional weight loss, low BMI, low levels of potassium, albumin and no nutrient intake for more than ten days (23). Early transition to oral diet is aimed to preserve the swallowing function. The subjective experience of the patient regarding nutritional intake is vital to meet the nutritional demands even after the completion of the treatment (24,25). The clinical guidelines recommend exercise interventions such as progressive resistance exercises, aerobic exercises, or a combination of them 2-3 times in a week to maintain mass and activity of skeletal muscles. Consider nutritional screening and the modification (if required) of the nutritional plan to be continued during the first post interventional year. Nutritional rehabilitation improves compliance with the treatment and clinical outcomes (26,27).

2. Nutritional Counselling in Head and Neck Malignancy Patients

Many of the severe symptoms caused by head and neck carcinomas and its treatment can be improved with proper diet and physical activity (28,29). Patients who get dietary and physical exercise counselling are better equipped to participate more actively in their care (30,31). Cancer patients can participate more actively in their therapy since they can change their diet and physical activity. Many patients are encouraged to do so, for example, by doing research or taking part in fitness regimens (32,33). Oncologists, family physicians and other medical professionals, nurses, nutritionists and physical therapists are among the healthcare professionals who counsel and promote nutrition and physical activity in cancer patients (34,35,36). However, a significant percentage of cancer patients still suffer from malnutrition or lack of physical activity, and every second cancer patient needs knowledge about healthy lifestyle choices (37,38,39). Multilevel interventions involving many health care practitioners are being used to improve nutrition and physical activity counselling (40,41,42).

3. An Update on Nutritional Interventional Studies in Head and Neck Malignancy Patients

Research was conducted on 166 malnourished advanced-stage cancer patients receiving chemotherapy who received whey protein supplements. 82 subjects were provided with highly purified, lactose-free, cysteine-rich cow milk whey protein of two sachets per day, constituting 20 gm/day, for a period of 3 months along with nutritional counselling. Statistically significant improvements in body composition, body weight, muscle strength, and reduced chemotherapy toxicity with improved treatment efficacy were observed when compared to 84 subjects of the control group (43). A study conducted with the aim of nutritional intervention in individuals with malignancy in the floor of the mouth and tongue. The nutritional group with 34 subjects received recommended high-energy soup with 1-1.2 kcal/1 ml with milk, a multivitamin, plus a probiotic, and the control group with 30 subjects received a mashing porridge with milk. The nutritional status of these study participants before and after surgery was assessed. The clinical symptoms, nutritional status, and quality of life in patients in the intervention group improved better than in the control group (44).

A clinical trial on 68 head and neck cancer patients who were randomized either to receive an oral nutrition supplement enriched with omega-3 fatty acids, probiotics, and micronutrients with a control group for a duration of 3 months. It was found that there was an improvement in body weight and serum albumin and prealbumin levels in patients with head and neck cancer cachexia in the intervention group (45). A randomized controlled trial conducted by Dai W et al. in the patients undergoing Head and Neck Cancer therapy. Based on their treatment histories, patients undergoing concurrent chemotherapy and radiation therapy were randomized to either the nutritional counselling group or the control group. Results indicate that the intervention group experienced a less significant decrease in serum total protein, serum albumin, transferrin, and the thickness of the triceps skin fold (46).

Sykes KJ et al. conducted randomized controlled trial on 49 head and neck cancer patients who were undergoing radiotherapy. This study concluded that optimizing preoperative nutrition has the potential to lessen the

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weight loss that patients with head and neck cancer typically undergo before surgery, particularly for those who have subjective dysphagia (47). A phase II clinical trial was reported by Dechaphunkul T et al. to assess the impact of immunonutrition in head of neck cancer therapy patients. 110 patients were randomized to receive either an isocaloric isonitrogenous control or an immunonutrient formula comprising dietary nucleotides, soluble fiber, omega-3-fatty acids, and arginine. The designated product was given to every patient five days in a row prior to each chemotherapy session. The immunonutrient and control groups' percentages of patients with severe oral mucositis were contrasted. Although the study's findings did not show a lower chance of developing severe oral mucositis, we did discover that immunonutrition may increase survival (48).

Barajas-Galindo DE et al. conducted a retrospective study on the patients who had undergone head and neck cancer surgery and were receiving enteral nutrition via a nasogastric tube during the postoperative phase. Analysis was done on how using immunoformula differed from using normal formulas. According to the study's findings, patients with head and neck cancer who get arginine-enriched enteral nutrition seem to have fewer postoperative fistulas, which shorten their hospital stays (49). A study conducted by Della Valle S et al. involved 54 patients receiving treatment for head and neck cancer is participating in a nutritional intervention. The study comprised patients with head and neck cancer who were candidates for chemoradiotherapy and who, in accordance with international recommendations, needed gastrostomy support for enteral nutrition. The goal of the nutritional intervention was to achieve 30 kcal/kg/d while taking oral intake and enteral nutrition into account. The research showed that in order to maintain constant body weight and phase angle both during and after treatment, a mean daily energy intake of 35 ± 10 kcal/kg was required (50).

A randomized clinical trial conducted by Cereda E et al. assess the effectiveness of nutritional counselling alone and nutritional counselling & supplements in head and neck cancer patients. Results of the trial concluded that the nutritional counselling with oral nutritional supplements is more effective than counselling alone as evidenced in better protein intake, maintenance of body weight and calorie intake in this group (51). Lages PC et al. conducted a double-blind clinical trial to assess the efficacy of the postoperative use of symbiotics in head and neck cancer patients. Test group received symbiotics through nasoenteric tube two times in a day on 1st to 5th and 7th day post operatively. Results of this trial concluded that there was no impact of these symbiotics on head and neck cancer patients' intestinal function and as well as on postoperative outcomes (52). A clinical study conducted by Mueller SA et al. to assess the impact of preoperative immunonutrition on post-surgical complications in head and neck cancer patients. A total of 96 patients divided into intervention group (51) and control group (45). Results of this study suggest that immunonutrition is effective in reducing the overall post operative complications (35.2% vs 58%) and also helped in reducing the days of hospital stay (17 vs 6 days) (53).

A prospective randomized trial was conducted on 44 head and neck cancer patients to assess the effectiveness of enteral glutamine postoperatively on the nutritional status of the patients. This study concluded that post operative supplements of enteral glutamine is effective in improving fat-free body mass, quality of life and serum albumin (54). A phase III clinical trial reported about effective of immunomodulating nutritional formula in patients who were undergoing chemotherapy for head and neck cancer. One hundred and eighty patients were randomized to receive oral supplementation (3 sachets/day) of either an isocaloric isonitrogenous control (control arm) or a formula supplemented with l-arginine and omega-3 fatty and ribonucleic acids (experimental arm). The incidence of acute mucositis and 36-month survival were compared using intention-to-treat and per-protocol analyses, as well as subgroup analyses of patients who were at least 75% compliant. Findings of this trial suggest that immunomodulating nutrition did not have any impact on the incidence of mucositis but has some impact on the survival of these patients in long term (55). Aeberhard C et al. reported a clinical study about the short-term effects of the immunonutrition in the head and neck cancer patients. This study included 411 patients. Immunonutrition significantly decreased hospital duration of stay (median hospital stay 6 vs. 8 days) and local infections. Patients who had undergone major surgery and radiation therapy in the past had more noticeable effects, according to subgroup analysis (56).

A clinical trial reported by Hanai N et al. about the efficacy of immunonutritional therapy using a supplement with a high blend ratio of omega-3 fatty acids in head and neck cancer patients during preoperative period. During the 28th day perioperative phase, the nutritional supplementation group was given two packs of Prosure®, an oral nutritional supplement fortified with eicosapentaenoic acid, daily. This trial concluded that the immunonutritional therapy, which used a nutritional supplement with a high mix ratio of omega-3 fatty acids does not have any impact on the nutritional status of patients with head and neck cancer (57).

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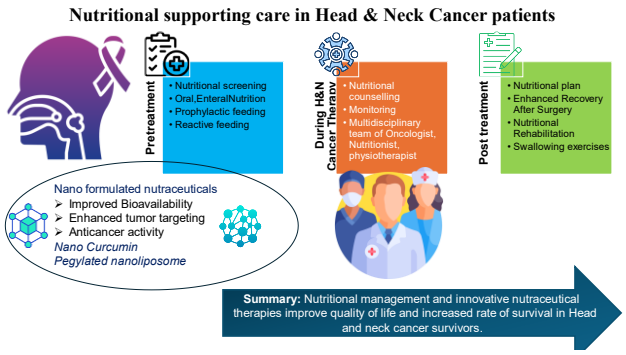

Figure 1. Schematic representation of study.

4. Therapeutic Efficacy of Nutraceuticals in Head and Neck Malignancies

i. Curcumin: As a bioactive compound found in turmeric with anti-inflammatory, antiseptic and antioxidant properties (58,59). Its mode of action is to inhibit epithelial mesenchymal transition, promotion of apoptosis, activation of NF-KB pathway which in turn regulates the COX-2, TNF-α, MMP, NOS, IL-6, IL-8, free radical scavenging activity, targets tumor angiogenesis and metastasis (60). Nano formulations are being explored to improve bioavailability (61,62). Capsules of Curcumin nano micelle 80mg twice a day for seven weeks were found to be effective in prevention and treatment of oral mucositis (63). Curcumin mouthwash was used in head and neck cancer patients for radiation induced oral mucositis (64). The mucoadhesive nanoparticles suspension loaded with curcumin were found to be effective in binding to the glycoprotein mucin in treatment of oral carcinoma (65). Nanocurcumin with registered product Sina curcumin was found to be effective in reducing radiotherapy induced mucositis in head and neck cancer therapy and can be recommended as a palliative care (66,67). Curcumin combined with chemotherapeutic agents demonstrated synergistic effects and anticancer activity (68).

ii. Green tea: Major phenolic compound epigallocatechin-3-gallate with potential chemo-preventive action (69). Epigallocatechin-3-gallate reduces the cell proliferation and spread of neoplastic cells in oral squamous cell carcinoma in a time and dose-dependent manner (70). After six months, individuals receiving treatment for oral cancer reported better oral health after using 100 mL of green tea mouthwash twice a day and swishing it for 60 seconds (71,72). A combination of green tea extract and curcumin demonstrated chemo preventive synergism with immune modulation of P53 and cyclin D1 biomarkers when compared to baseline in potentially malignant oral disorder patients(73,74).

iii. Resveratrol: A natural polyphenol and phytoalexin found in grapes with anticancer, anti-inflammatory, anti-oxidant action (75,76,77). It downregulates Signal Transducer and Activator of Transcription signaling pathway and inhibits proliferation and induces apoptosis (78). Nano formulations with improved bioavailability and enhanced tumor targeting of resveratrol such as lipids, glycan, synthetic polymers and proteins were developed in cancer therapeutics (79). Pegylated nanoliposome is a combination of resveratrol with chemotherapeutic agent 5-fluorouracil which improves chemotherapeutic efficacy and enhanced cytotoxicity in comparison to free drugs against head and neck squamous cell carcinoma cell lines (80).

5. Conclusion

High prevalence of malnourishment was observed in patients with head and neck cancer prior to initiation of cancer treatment. Nutritional screening and providing essential nutritional requirements to the head and neck cancer patients was found to be challenging even if the multidisciplinary team of specialists was involved. Continuous monitoring with supportive care strategies and providing nutritional care before, during, and after the cancer treatment not only improves the quality of life but also the survival rates of these patients. Further research is required to assess the role of novel nano formulations in targeting delivery to maximize the therapeutic yield with minimum adverse effects of the drug and to reduce chemotherapeutic drug resistance. A Schematic representation of study has been provided in **Figure 1**.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to authorship and/or publication of this article.

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