

# Nutritional Implications in Head and Neck Cancer - A Review

## Review Article

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### Abstract

Cancer is a complex disease wherein mutations in protein-encoding genes lead to numerous tempo-spatial changes in cell physiology, ultimately leading to malignant tumors. Indian Population Based Cancer Registries documents incidences of cancers across the country and it was reported that highest Age Adjusted Rates was found in cancers of the tongue, hypopharynx and oesophagus which are head and neck cancers. They are amongst the commonest malignancies, accounting for approximately 20% of the cancer burden in India, tobacco and alcohol are the two major risk factors. Common acute reactions experienced during radiotherapy are dysgeusia and fatigue, which may cause cancer cachexia. These patients have one of the highest malnutrition prevalence rates, which affects physical function and quality of life with 25-50% of these patients classified as nutritionally compromised prior to commencement of treatment. Minimizing weight loss for patients at nutritional risk is a major goal of nutritional management. It is important to replenish the protein and energy intakes along with the micronutrients. Common nutrition goals for surgical patients include symptoms management, weight maintenance, preservation of functional status and body composition which can be attained by modulation of dietary components, addition of oral nutritional supplements, or provision of enteral or parenteral nutrition. Recent studies have shown that Enteral nutrition support via percutaneous endoscopic gastrostomy administered to the patients help in preventing weight loss, dehydration, nutrient deficiencies, treatment interruptions, hospitalizations and improving quality of life. Successful management of these patients requires orderly care and follow-up by a multidisciplinary nutrition team.

**Keywords:** Head and Neck Cancer; Quality of life; Malnutrition; Nutrition care

### Abbreviations

AARs: Age Adjusted Rates; ADA: American Dietetic Association; AJCC: American Joint Committee on Cancer; CHOs: Carbohydrates; CT: Computed Tomography; DNA: Deoxyribonucleic Acid; EC: Esophageal Cancer; ESPEN: European Society of Parenteral and Enteral Nutrition; HNC: Head and Neck Cancer; HNSCC: Head and Neck Squamous Cell Carcinoma; HPV: Human Papilloma Virus; IARC: International Agency for Research on Cancer; ICMR: Indian Council of Medical Research; MRI: Magnetic Resonance Imaging; NCRP: National Cancer Registry Programme; NG: Nasogastric; NRI: Nutrition Risk Index; PBCRs: Population Based Cancer Registries; PEG: Percutaneous Endoscopic Gastrostomy; PET: Positron Emission Tomography; PG-SGA: Patient Generated-Subjective global Assessment; PNI: Prognostic Nutrition Index; QoL: Quality of Life; RIG: Radiologically Inserted Gastrostomy; SCC: Squamous Cell Carcinoma; SF-36: Short Form-36; SIG: Surgically Inserted Gastrostomy; TNM: Tumor Node Metastasis; TPN: Total Parenteral

Nutrition; UICC: Union for International Cancer Control; UV: Ultraviolet; WHO: World Health Organization

### Introduction

Cancer is a complex disease involving abnormal cell growth (neoplasia) and numerous tempo-spatial changes in cell physiology, which ultimately lead to malignant tumors. Tumor cells are invasive in nature which spread to the surrounding tissues and distant organs causing high rates of morbidity and mortality [1]. These altered cells no longer require special signals to induce cell growth and division as the processes regulating normal cell division are disrupted. Abnormalities such as change in cell structure, decreased cell adhesion, and production of new enzymes in cancer cells usually result from mutations in protein-encoding genes that regulate cell division [2]. The development of cancer is a multistep process that occurs in three stages: initiation, promotion, and progression [3]. The biological process by which normal cells are transformed into malignant cancer cells has been the subject of a large research effort

in the biomedical sciences for many decades. Malnutrition in cancer patients, also known as Cancer cachexia is due to cytokine-induced metabolic derangements. Patients with HNC have one of the highest malnutrition prevalence rates among all diagnostic groups, with 25-50% of these patients classified as nutritionally compromised prior to commencement of treatment. Oncological therapies such as Radiotherapy and Chemotherapy further worsen the nutritional status of cancer patients, thereby making nutrition an important component of medical care. Weight loss during radiation therapy to the head and neck can diminish the safety and effectiveness of the treatment. Impaired nutritional status is associated with decreased QoL, physical function, and survival and therefore, with increased personal, social and healthcare costs [4]. Because of the complex, multifactorial nature of disease-related malnutrition, it is often very challenging to conduct high-level clinical nutrition studies. In India, literature on nutrition screening and the impact of nutrition interventions in cancer patients is limited. Commercially available formulations are high in cost and are not disease specific; therefore there is a need to formulate a low cost food formulation using functional ingredients which could meet the nutritional needs and reduce the financial burden of cancer patients in India. Since most of the patients with HNC are unable to take food orally, the formulation should be suitable both for oral and enteral feeding. Researchers are also focusing on medicinal plants with anti-cancer properties and its utilization as a nutraceuticals.

### Types of Head and Neck Cancer (HNC)

The head and neck region comprises a variety of anatomic sites. HNC affects moist mucosal surfaces like the mouth, throat and nose. Tumors arising from the skin, nasal cavity and paranasal sinuses, oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, esophagus, thyroid gland, salivary glands, soft-tissue tumors, bone sarcomas, and miscellaneous tumors such as neurogenic tumors and paragangliomas are all generically included in the head and neck region [5]. Laryngeal cancer includes tumors of the supraglottis, glottis and subglottis; Hypopharyngeal cancer affects postcricoid area, pyriform sinus and posterior pharyngeal wall; Oropharyngeal cancer affects the base of tongue, tonsil and soft palate; Oral cavity cancer includes tumors of the buccal mucosa, retromolar triangle, alveolus, hard palate, anterior two-thirds of tongue, floor of mouth and mucosal surface of the lip [6].

### Causes and Risk Factors of HNC

The transformation from a normal cell into a tumor cell is a multistage process, typically a progression from a pre-cancerous lesion to malignant tumors. These changes are the result of the interaction between a person's genetic factors and three categories of external agents, including:

- physical carcinogens, such as ultraviolet and ionizing radiation;
- chemical carcinogens, such as asbestos, components of tobacco smoke, aflatoxin (food contaminant) and arsenic (drinking water contaminant); and
- biological carcinogens, such as infections from certain viruses, bacteria or parasites.

WHO, through its cancer research agency, IARC, maintains a classification of cancer causing agents [7].

### Risk Factors of HNC

**a. Viruses:** HNC associated with Human Papilloma Virus (HPV) infection is increasing. In a systematic review by Kreimer et al, 5046 cases of SCC were identified from 60 eligible studies from 26 countries. These included 2,642 cases from the oral cavity, 969 cases from the oropharynx, and 1,435 cases from the larynx. Twenty-six percent of all HNSCC biopsy specimens were HPV positive. Overall HPV prevalence was significantly higher in oropharyngeal SCCs (35.6%) than in oral SCCs (23.5%) and laryngeal SCCs (24.0%). HPV16 was the most common type detected which was present in 30.9% of oropharyngeal SCCs, 16.0% of oral SCCs, and 16.6% of laryngeal SCCs. HPV16 thus accounted for 86.7% of all HPV-positive oropharyngeal SCCs compared with 68.2% of HPV-positive oral SCCs and 69.2% of HPV-positive laryngeal SCCs. HPV18 was the next most common oncogenic HPV type detected and was detected in 8.0% and 3.9% of oral and laryngeal SCCs, respectively, yet was only present in 1.0% of oropharyngeal SCCs [8].

**b. Tobacco:** The relationship between cigarette smoking and regular exposure to tobacco smoke with various types of cancers is known. The use of other tobacco products, such as chewing tobacco, is linked to cancers of the mouth, tongue and throat. In a study, the effect of use of powdered tobacco (Khaini tobacco) with the addition of lime used by the residents of Bihar, India was studied. The tobacco/lime mixture is usually placed on the inner side of the lower lip within the gingivolabial groove. Carcinomas (so-called "Khaini cancers") develop mainly at the site where the tobacco is in close contact with the mucosa. The micronucleus test on exfoliated cells provided evidence of carcinogen exposure in the tissue from which cancer developed [9]. Epidemiologic studies suggest a strong association between smokeless tobacco and oral carcinogenesis. However, the risk of cancer decreases soon after a smoker quits, while precancerous conditions often diminish after a person stops using smokeless tobacco [4].

**c. Alcohol:** Heavy drinkers face an increased risk of cancers of the mouth, throat, esophagus, larynx and liver. Some studies suggest that even moderate drinking may slightly increase the risk of breast cancer. All cancers caused by cigarette smoking and heavy use of alcohol could be prevented completely. A case control study of combined effect of tobacco and alcohol on laryngeal cancer risk was studied which suggested that there was an increased multiplicative risk of cancer with use of cigarette smoking and alcohol intake [9,10]. HNC tends to be more common in males. The most notable modifiable risk factors for developing HNC include the use of tobacco and /or marijuana; and frequent heavy consumption of alcohol. Use of alcohol potentiates tobacco-related carcinogenesis which is also an independent risk factor [4].

**d. Paan (betel quid):** Immigrants from Southeast Asia who use paan (betel quid) have increased risk of oral cancer [11]. Betel nut chewing is associated with oropharyngeal cancer. A long term usage of betel nut causes "betel chewer's perleche," consisting of fissures at the angles of the mouth produced by constant moistness

and maceration. A unique type of leukoplakia is seen in the gingival area. This can progress to SCC of the oral cavity and esophagus. The calcium hydroxide component and arecaidine have subsequently been shown to cause submucosal fibrosis, a precancerous oral lesion that has been associated with an increased incidence of SCC. It is also observed that betel nut acts synergistically with tobacco to produce oral cancer [12].

**e. Diet:** Dietary factors have a dual role to play both in enhancing or reducing the risk of cancer. Several nutritive and non-nutritive dietary constituents are reported to increase the risk of cancer. Consumption of maté, a tea-like beverage habitually consumed by South Americans, has been associated with an increased risk of cancers of the mouth, throat, esophagus and larynx [13]. Consumption of certain preserved or salted foods during childhood is a risk factor for nasopharyngeal cancer observed in elevated rates in natives of Southeast Asia, Arctic region, the Arabs of North Africa and parts of the Middle East [14].

Dietary factors have a role in reducing the risk of cancer. Epidemiologic data suggest a protective role of dietary carotenoids and an inverse association between the consumption of fruits and vegetables and the incidence of HNC. The specific protective components in these foods remain to be elucidated [15].

**f. Occupational exposure:** Occupational exposure to wood dust is a risk factor for nasopharyngeal cancer [16]. Exposure to chemicals such as dyes, solvents, pesticides, polycyclic aromatic hydrocarbons, chlorine etc have been associated with oral and pharyngeal cancer; and formaldehyde, bleaches, varnishes, adhesives and biocides with nasopharyngeal cancer. Exposure to glass fibres, coal particles and asbestos were associated with risk of hypopharyngeal cancer [17].

**g. Radiation exposure:** Radiation to treat the first primary cancer during childhood have a 39 fold higher risk to develop second primary salivary gland cancer [18].

**h. Oral health:** Poor oral hygiene, periodontal disease, chronic candidiasis, HPV and herpes virus infections link statistically with cancer. Infections may trigger cell proliferation, inhibit apoptosis, interfere with cellular signaling mechanisms and up-regulate tumor promoters. In addition, several oral micro-organisms metabolize alcohol to carcinogenic acetaldehyde thus explaining the association between poor oral hygiene, alcohol consumption and carcinogenesis [19].

Thus, to reduce or prevent these risk factors, consuming a balanced diet that meets fruit and vegetable dietary recommendations, avoiding or limiting alcohol consumption, and avoiding smoking appear to decrease the risk of developing HNC [4].

#### Incidences of HNC in India and Worldwide

The NCRP of the ICMR documents incidences of cancers. A comparison of the AARs of Indian PBCRs with the AARs of International PBCRs from five different continents viz. Africa, Asia, Australia, Europe, North America and South America available on cancer incidence was reported by the NCRP for the period 2009 to 2011. Two registries from each continent demonstrating the highest

AAR had been taken for comparison with the top five AARs among Indian PBCRs for all sites and selected sites of cancer. It was observed that highest AAR was seen among the Black males (519.9) population of Detroit, Michigan State, USA, whereas in females (389.3) highest AAR was seen in Goiana, Brazil [20]. The incidence of HNC varies widely across the world. Regions of high HNC include much of Southern Asia and parts of Central and Southern Europe. High incidence rates were reported from developing nations like India, Pakistan, Bangladesh, Taiwan and Sri Lanka. While an increasing trend has been observed in Pakistan, Taiwan and Thailand, a decreasing trend is seen in Philippines and Sri Lanka. The most common age of occurrence of cancer in different parts of oral cavity is usually between 51-55 years in most countries. Tongue is the leading site among oral cancers in India. The next most common sites in Asian countries include the buccal mucosa and gingiva [21]. Worldwide HNC statistics indicate that there are 6,40,000 cases of HNC per year, resulting in approximately 3,50,000 deaths per year. Cancer of the oral cavity and pharynx are the most common type of HNC with approximately 4,80,000 cases per year and about 1,60,000 cases of larynx per year [22]. HNC is the sixth most common cancer worldwide.

HNCs are amongst the commonest malignancies, accounting for approximately 20% of the cancer burden in India. The major risk factors are tobacco chewing, smoking and alcohol consumption, which are all preventable. In India, Aizawl district had higher AARs in both males (273.4) and females (227.8) among the PBCRs. Indian PBCRs had highest AARs in cancers of the tongue, hypopharynx and oesophagus [20]. The incidences differed regionally with greater incidences of cancers of Mouth (12.3%) and Lung (8%) in Mumbai; Hypopharynx (8.4%) and Oesophagus (7.9%) in Bangalore; Stomach (9.2%) and Lung (8.9%) in Chennai, in males. An average of 22.76% of Breast cancer and 22.06% of Cervix cancer was observed in all regions in females [23]. According to a study, malignant cases in Bihar, India were common in males than in females with male: female ratio of 3.1:1. This observed incidence patterns are a reminder of widespread unawareness, low healthcare utilization with virtually non-existent cancer programs [24].

In another study, an estimation of newer cancer cases by 2026, in India, was done by Neevan et al. In India, in 2011, nearly 1,193,000 new cancer cases were estimated with a higher load among females (603,500) than males (589,800). It was estimated that the total number of new cases might increase from 0.589 million in 2011 to 0.934 million by 2026 in males and 0.603 to 0.935 million in females. When adjustments for increasing tobacco habits and increasing trends in many cancers are made, the estimates may further increase [25]. From these studies it can be observed that the cases of Head and Neck Cancers are increasing in India.

#### Diagnosis and Staging of HNC

Routine physical examination, including a thorough oral examination, is the best way to detect HNCs before they become symptomatic. Definitive diagnosis usually requires a biopsy. Additional information can be obtained from a combination of imaging tests, such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI) or Positron Emission Tomography

(PET), endoscopy and fine-needle aspiration of any neck mass [26]. Head and neck cancers are staged according to size (T) and site of the primary tumor, the presence of metastases in the cervical lymph nodes (N), and evidence of distant metastases (M). Staging usually requires imaging tests [26].

TNM is an anatomic staging system that describes the anatomic extent of the primary tumor, involvement of regional lymph nodes and distant metastasis. Revisions to the TNM staging system have been based on natural history of tumors at various sites aided by advances in technology that have allowed clinicians to better assess the extent of tumors. The majority of mucosal HNCs are SCCs. Therefore, the TNM classification of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) for most mucosal anatomic sites is designed for SCC and minor salivary gland cancers. For many decades, the AJCC-UICC TNM staging system has been used for staging HNC worldwide and the sixth version is the latest. In current practice, information obtained from clinical examination and radiologic imaging is used to assign a clinical stage (cTNM), which is then used to stratify patients for selection of therapy and to report outcomes of treatment. If the patient undergoes surgical resection, the pathologic stage (pTNM) derived from histopathologic examination of the tumor and/or regional lymph nodes are useful in selecting postoperative adjuvant therapy and for prognosis [5].

### Common Complications In HNC Patients

#### Swallowing problem

Cancer treatment can cause mouth and throat problems. Swallowing requires movement of the lips, tongue, palate, throat, larynx and oesophagus. Surgery or radiation therapy may render severe dysfunction of the base of the tongue, larynx and pharyngeal muscle causing different types of swallowing problems due to which highest rate of malnutrition is observed in HNC patients [27].

#### Treatment induced complications

Complications associated with radiotherapy of the head and neck region deleteriously affects the salivary glands, oral mucosa, bone, dentition, masticatory musculature and temporomandibular joints due to which clinical consequences such as mucositis, hyposalivation, taste loss, osteoradionecrosis, radiation caries, fibrosis and trismus occurs. Mucositis and taste loss are reversible consequences whereas hyposalivation is irreversible [28].

Most patients with head and neck carcinomas, treated with a curative intent, receive a dose between 50 and 70 Gy [28]. RT is generally given 5 times per week at the rate of 2 Gy per day for 6-7 weeks. The associated complications and side effects escalate with time and continue to worsen beyond the completion of therapy.

Slow healing and infection are indirect complications of cancer treatment. Both chemotherapy and radiation therapy can stop cells from dividing and slow the healing process in the mouth. Chemotherapy associated symptoms include nausea, vomiting, constipation and mucositis. It may decrease the number of white blood cells and weaken the immune system thus, predisposing to infections [4,29].

**Table 1:** Side effects associated with Radiation therapy at different doses [27,28].

Dose of radiation therapy	Occurrence of side effects	Side effects
< 10 Gy	1 <sup>st</sup> week	Mucositis and hyperkeratinization
10 - 20 Gy	2 <sup>nd</sup> week	Erythema of the skin, pseudomembranous mucositis, ulceration, microbial infection and atrophy of taste buds.
20-30 Gy	3 <sup>rd</sup> week	Taste changes ,mucositis, decreased amylase secretion paralleled by acinar cell loss and decreased salivary flow and change in salivary composition
30-50 Gy	Upto 3 months	Taste alterations, dermatitis, change in the oral microflora causing dental caries and significant reduction in salivary flow, thyroid dysfunction.
50-70Gy	3 – 6 months	Dysgeusia, Xerostomia, Fibrosis, Stenosis, Muscular atrophy, cranial neuropathy, Osteoradionecrosis

### Cancer Cachexia

The term cancer cachexia is derived from the Greek words kakos and hexis meaning poor condition. Cachexia has been defined as a syndrome characterized by the progressive loss of lean tissue and body fat, and losses are often in excess to that explained by the associated anorexia. There are often additional metabolic derangements, including anaemia, acute phase protein response and alterations in plasma lipid profile [30]. Weight loss due to starvation differs significantly from weight loss due to cancer cachexia. Loss of weight in cachexia is due to cytokine-induced metabolic derangements such as insulin resistance, increased lipolysis and increased protein turnover which leads to decreased appetite, weight loss, and metabolic alterations. Although there is no definitive method for diagnosing cancer cachexia, clinical signs of anorexia, muscle wasting and unintentional weight loss of 5% or more of body weight in 6 months not due to mechanical obstruction, treatment, side effects are suggestive of cancer cachexia [31].

### Weight loss

Weight loss due to obstruction, treatment, or/and side effects, that is expected to cease once treatment is ceased, should not be described as cachexia, but rather as due to inadequate dietary intake. The causes of weight loss in patients with HNC are multifactorial and may be due to reduced intake, treatment related or mechanical obstruction, or cachexia. Symptoms such as anorexia, depression, anxiety, fatigue, early satiety and pain can result in a decreased appetite and food intake. Cancer treatment may result in weight loss, for example surgery (malabsorption), radiotherapy (nausea, pain, diarrhea, mucositis), and chemotherapy (nausea, vomiting, constipation, mucositis). Appropriate nutrition support provided during radiotherapy can help to overcome some of the nutrition impact symptoms and help patients to maintain weight compared with standard practice where patients continued to lose weight during radiotherapy treatment [32].

### Nutritional Challenges Associated With HNC

The continuum of cancer survival includes treatment and recovery as well as living with advanced cancer. Each stage is associated with different needs and challenges for the patients, caregivers, and clinicians. Both cancer and the oncological therapies utilized for its treatment can have profound effects on an individual's nutritional status, thereby making nutrition an important component of medical care [3].

### Effect of Malnutrition on HNC

Patients with HNC have one of the highest malnutrition prevalence rates among all diagnostic groups, with 25-50% of these patients classified as nutritionally compromised prior to commencement of treatment [33]. Weight loss during radiation therapy to the head and neck can diminish the safety and effectiveness of the treatment. Significant amounts of weight loss can also affect the chemotherapy regimen, preventing the patient from receiving the optimal dosage. Involuntary weight loss greater than 5% in one month, or more than 1-2% per week, is a reliable indicator of malnourishment. Despite awareness, malnutrition continues to contribute to significant morbidity during and after therapy and impedes aggressive intervention. Because of the complex, multifactorial nature of disease-related malnutrition, it is often very challenging to conduct high-level clinical nutrition studies. However, patients demonstrate better physical function and QoL with nutritional intervention compared to the usual care [4]. Malnutrition may not be a nutritional risk factor for all cancer patients however, nutritional screening, assessment and monitoring are crucial to prevent or minimize the development of malnutrition at every stage of treatment.

### Nutrition Impact Symptoms (NIS)

NIS in patients with HNC may be attributable to tumor itself or may be side effects of the cancer treatment. The factors most significantly associated with nutritional status include tumor stage, tumor location, time since diagnosis, dietary intake, and previous treatment [4].

NIS such as nausea, vomiting, diarrhea, constipation, pain, anxiety, oropharyngeal mucositis, dysgeusia, xerostomia and fatigue during radiotherapy compounded by the addition of chemotherapy with other multimodality therapies are generally associated with increased toxicity which may be experienced even as long as 12 months following commencement of therapy and have been associated with reductions of Quality of Life (QoL) [34]. Because of the expected toxicities, malnutrition in patients with HNC is a serious clinical concern [35]. Impaired nutritional status due to improper food intake is associated with decreased QoL, physical function, and survival and therefore, with increased personal, social and healthcare costs. The functions of eating and drinking play a large role in social activity and participation hence decreasing the QoL in HNC patients. A study suggests that QoL shows better outcome than clinical outcomes alone [4]. Patients with cancer cachexia reported alterations in the body image which negatively affected their self-esteem, relationships, spirituality, physical activity and social functioning [3].

### Dysphagia

Swallowing function often deteriorates but then improves for as long as 12 months post-treatment. Swallowing function may stabilize with time but often remains poorer than prior to treatment. Studies show that severity of dysphagia in some patients with HNC is correlated with compromised QoL, depression, and anxiety. Anecdotal evidence suggests that some patients with HNC will require dietetic and speech pathology support for months after treatments and may not ever return to managing a normal diet without supplementation [4].

### Nutritional Management of HNC

#### Goals of Nutritional management in HNC

Considering the treatment related and nutritional complications discussed earlier, the major goals of nutritional management should be maintenance of body weight, minimizing weight loss preventing or minimizing nutritional deficiencies, preserving muscle tissue, minimizing nutrition-impact symptoms such as decreased appetite, nausea, bowel function changes; and maximizing QoL. Appropriate dietary intake ameliorates treatment related side effects such as early satiety, fatigue and anorexia. Professional practice suggests it is easier to prevent or slow the malnutrition trajectory than to reverse chronic malnutrition. In weight-losing patients with inadequate dietary intake, nutrition support (dietary counseling with or without supplements) should be provided to improve or maintain nutritional status and QoL. Patients should be initiated with nutritional management on presentation, prior to treatment; to avoid nutritional depletion. All patients with HNC should be regarded as being "at risk" for nutritional deficiencies irrespective of their tumor stage. Unfortunately, because of the limited resources available for nutrition diagnosis and treatment, referral of high-nutritional-risk patients is not always done consistently in practice [4].

The primary nutritional goal of addressing inadequate oral intake in these patients is to increase dietary intake to a level sufficient to meet their requirement. In addition to providing adequate energy and protein intake to meet the requirements, other agents for limiting cachexia have been investigated, including eicosapentanoic acid and other pharmacotherapies [4].

Prior to treatment, nutrition assessment should be conducted using a valid a reliable nutrition assessment tool, which will be useful to assess nutritional status, guide nutrition intervention, and monitor outcomes in patients with cancer. Appropriate nutritional management and physical recommendations before, during and after treatments should be implemented to ensure best patient care and optimal outcomes [4].

### Nutrition screening

Nutrition screening helps in identifying the nutritional risks and needs to plan suitable nutrition support to the target group. Nutrition screening is effective only with a formal, systematic nutrition assessment in patients. Significant weight loss is suggestive of a poor prognosis and also associated with decreased physical function, QoL and treatment schedules. Maintaining adequate nutrition during treatment requires considerable commitment and motivation for

most patients. Patients without support at home to prompt feeding at regular intervals are more likely to find maintaining adequate intake difficult [35]. Malnutrition Screening Tool (MST) has been used in the cancer population to identify those patients who are at greatest risk for developing nutritional problems [36].

### Nutrition Assessment tools in Common use

Very few validated tools have been available to assess the nutrition status in patients with cancer. The commonly used tools by researchers and clinicians are Malnutrition Screening Tool (MST), Subjective Global Assessment (SGA), Patient Generated- Subjective Global Assessment (PG-SGA), Nutrition Risk Index (NRI), Short Form-36 (SF-36) and The European Organization for Research and Treatment of Cancer questionnaire (EORTC); The Eastern Cooperative Oncology Group (ECOG) performance status scale to assess the functional status.

There are various tools used in assessing the nutritional and functional status of HNC patients:

According to the American Dietetic Association (ADA), an effective nutrition screening tool should be:

- Simple, quick, reliable, valid and inexpensive
- Easily administered with minimal nutritional expertise
- Applicable to most patients and designed to incorporate only routine data and tests available on admission.

**MST:** It is a five step screening tool to evaluate adults, who are malnourished, at risk of malnutrition or obese. It also includes guidelines which can be used to develop a nutrition care plan [36].

**PNI:** Using parameters such as serum albumin, serum transferrin, triceps skin fold, and delayed hypersensitivity, the PNI was developed and is calculated as:

$$\text{PNI}\% = 158\% - 16.6(\text{ALB}) - 0.78(\text{TSF}) - 0.2(\text{TFN}) - 5.8(\text{DH}) [37].$$

[ALB = albumin (g/dL); TSF = average of three triceps skin fold measurements (mm); TFN = serum transferrin (mg/dL); DH = number of positive delayed hypersensitivity responses measured at 24 and 48 hours after intradermal injection of five antigens (Candida albicans, mumps, tuberculin purified protein derivative, Trichophyton, and streptokinase-streptodornase). Major post-operative complications occurred in patients with a PNI > 20. In another study, a PNI > 40 indicated a high risk of developing a post-operative infection].

**NRI:** It uses parameters such as serum albumin concentration and the ratio of actual to usual weight and was originally developed in AIDS and cancer patients [38,39]. The NRI formula is calculated as:

$$\text{NRI} = (1.519 \times \text{serum albumin, g/dL}) + \{41.7 \times \text{present weight (kg)/usual body weight(kg)}\} [40].$$
 [From these NRI values, four grades of nutrition-related risk are defined: i) major risk (NRI<83.5); ii) moderate risk (NRI 83.5-97.5); iii) mild risk (NRI 97.5-100); iv) No risk (NRI > 100). The NRI cut-off values are determined according to weight losses of 5%, 10% or 20%].

**PG-SGA:** It is a modification of an earlier tool called SGA. It

has two sections: a patient-completed section which includes data regarding weight history, symptoms, dietary intake and activity level; and a section completed by the healthcare professional, who evaluates metabolic demand considers disease in relation to nutritional requirements and incorporates a physical assessment [41].

**EORTC QLQ-C30:** It is a questionnaire developed to assess the quality of life of cancer patients. It is supplemented by disease-specific modules for e.g. Breast, Lung, Head & Neck, Esophageal, Ovarian, Gastric, Cervical cancer, Multiple Myeloma, Oesophago-Gastric, Prostate, Colorectal Liver Metastases, Colorectal and Brain cancer [42].

**ECOG performance status scale:** It is used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis [43].

**SF-36:** The SF-36 is a measure of health status and is commonly used in health economics as a variable in the quality-adjusted life year calculation to determine the cost-effectiveness of a health treatment. It consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The eight sections are vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health [44].

## Nutrition Assessment

### Anthropometric assessment

Anthropometric measurements such as patient's height, weight, and body mass index are considered relevant and objective measures of a cancer patient's nutritional status with few potential errors in measurement in a clinical setting. Body weight and weight history are essential components of the initial nutritional assessment due to the significant impact of weight loss and underweight on morbidity and mortality.

Other parameters such as skinfold (TSF), circumference measurements (MUAC, MUAMC) and bioelectrical impedance technology for measuring body composition have been used in clinical settings to measure lean body mass and body fat distribution. However, these methods suffer from errors due to measurement, unless performed by well-trained clinical staff and do not provide meaningful data of efficacy on nutritional therapy [45].

### Biochemical assessment

Several biochemical parameters such as haemoglobin, fasting blood sugar, albumin, transferrin, total blood count, lymphocytes, creatinine, serum urea and certain tumor markers such as TNF- $\alpha$ , IL-6, p53, NF- $\kappa$ B, etc can be used to determine the nutritional status and prognosis of the disease [45].

### Dietary assessment

A detailed dietary assessment is indicative of the actual food and nutrient intake of the patients which helps the nutritionist/clinician to provide individualized nutrition care to improve the nutrition status

or ameliorate the effects of cancer therapy. It also gives information on malnutrition associated with reduced food intake.

The dietary intake of cancer patients has to be assessed frequently i.e., random, weekly, 2 weekdays + 1 weekend day, 24-h dietary recalls (gold standard for collecting dietary data) using a five-step multipass procedure. Nutritional history should include habitual diet and any change in diet pattern, frequency of meals or snacks, quantity of food at meals, self-imposed food restrictions, use of supplements, and other complementary therapies and vitamin/ mineral use [45].

### Functional assessment

In addition to more objective measurements by speech-language pathologists, the M.D. Anderson Dysphagia Inventory (MDADI) measures the impact of dysphagia on QoL with regard to social function and is known to have greater degree in identifying swallowing-related disability in patients with HNC [46].

### Nutrition Support

Evidence suggests that, the nutritional and non-nutritional components in the diet reduce initiation and promotion of malignant growth. Diets are often deficient in micro nutrients such as  $\beta$ -carotene, vitamin A, riboflavin, folic acid, vitamin C, iron, zinc and selenium, which are claimed to be potent protective agents that act by suppressing carcinogenesis [47]. Research studies confirm that in patients undergoing cancer treatment, the mean nutrient intake and percent adequacy for all nutrients were much lower than the RDA because of swallowing difficulty and treatment associated complications [47].

### Routes of Intervention

#### Oral intake

The preferred method of nutrition intervention, the least expensive and least invasive, is a standard or modified diet plus oral supplementation. Several options of commercial and homemade recipes are recommended as tolerated and/or preferred by the patients. Several pharmacological and non-pharmacological strategies to improve appetite and nutritional intake and prevent early satiety are developed with individual patients. However, if patients are unable to consume sufficient protein and calories for greater than 7-10 days with continued decline in nutritional status as indicated by serum hepatic proteins, weight loss, and anthropometrics, alternate means of support via enteral nutrition (EN) or total parenteral nutrition (TPN) may be indicated [48].

#### Tube feeding

Evidence suggests that early introduction of tube feeding in patients unable to manage sufficient dietary intake will ensure nutrition support and may prevent weight loss.

EN: When nutrition management symptoms cannot be adequately managed to allow for oral intake sufficient to meet dietary requirements, enteral feedings are highly effective in increasing energy, protein and micronutrient intake and maintaining body weight compared with dietary intake alone. Currently, there are no universally accepted guidelines identifying patients who require tube

feeding [4]. The literature, however, identifies EN procedures such as Surgically Inserted Gastrostomy (SIG), Percutaneous Endoscopic Gastrostomy (PEG), Radiologically Inserted Gastrostomy (RIG) and Nasogastric (NG) tube feeding methods for HNC. Supporting evidence favors PEG than other EN procedures viz., RIG, SIG and NG with respect to the rates of serious complications and deaths, the only drawback being the cost and duration of enteral feeding [49-53].

TPN: It is beneficial in severely malnourished and metastatic cancer patients. TPN is composed of dextrose, amino acids and lipid emulsion at different concentrations.

In a study on the nutritional and metabolic effects of TPN and EN in cachectic cancer patients, an optimum nutritional support with TPN providing energy at 35 to 55 kcal/ kg and 1.2 to 2.0 g of amino acids/kg daily was beneficial in stimulating whole body protein synthesis, increase in thyroxin-binding prealbumin and retinol-binding protein; decrease skeletal muscle protein catabolism with an improvement in lean body mass and visceral proteins whereas EN providing energy at 35 kcal/kg and 1.3 g of amino acids/kg improved lean body mass and visceral proteins and at least 42 kcal/kg and 2.3 g of amino acids/kg improved some immune responses [54].

Three randomized studies were performed to compare TPN and EN, and conflicting results were obtained. Only TPN showed some significant advantages with regard to weight gain, nitrogen balance, maintenance of serum albumin levels and some mineral balances. When comparing TPN to a standard oral diet; body weight, nitrogen balance, 3-methylhistidine urinary excretion, and serum levels of transferrin, cholinesterase, thyroxin-binding prealbumin and retinol-binding protein improved with the nutritional support. TPN is therefore beneficial to prevent deterioration of nutritional status [54].

### Nutrient Requirements

#### Energy

Malignancies exert a metabolic effect on the host; however, the difficulty lies in predicting to what degree metabolic rate is affected due to the great variability in individual response as well as type of cancer and combination of therapies. Studies have measured the basal energy expenditure in a variety of cancer patients.

Squamous cell carcinoma of the head and neck is associated with significant weight loss prior to, during, and after cancer diagnosis and treatment which needs an effective nutritional intervention using appetite stimulants, dietary counseling, and prophylactic enteral tube feeding to meet compromised nutritional needs in patients receiving radiation and/or chemotherapy [55]. The energy requirements can be calculated using Harris benedict equation [56]:

Basal energy expenditure (BEE)

For females:  $55(9.6 \times \text{wt in kg}) + (1.7 \times \text{ht in cm}) - (4.7 \times \text{age})$

For males:  $66.5(13.7 \times \text{wt in kg}) + (5 \times \text{ht in cm}) - (6.8 \times \text{age})$

For weight maintenance needs:  $\text{BEE} \times 1.15 - 1.3$

For weight anabolism needs:  $\text{BEE} \times 1.5$

Daily calories for cancer patients vary between 25 to 35 calories per kg body weight (k.b.w) depending on the physical activity i.e, whether the patient is bedridden or ambulant.

### Carbohydrates

Evidence suggests that reducing the amount of dietary carbohydrates (CHOs) could suppress the emergence of cancer and proliferation of already existing tumor cells. This hypothesis is supported by the association between modern chronic diseases like the metabolic syndrome and the risk of developing or dying from cancer. Glucose, end product of CHO digestion, can have direct and indirect effects on tumor cell proliferation. Most malignant cells depend on steady glucose availability in the blood for their energy and biomass generating demands and are not able to metabolize significant amounts of fatty acids or ketone bodies due to mitochondrial dysfunction [57]. There are no recommended dietary allowances for carbohydrates in cancer patient populations.

### Protein

Protein needs of cancer patients range from 1-1.2 g per k.b.w daily for non-stressed patients, 1.2-1.6g per k.b.w daily for hypercatabolic cancer patients and 1.5-2.5g per k.b.w daily for severely stressed cancer patients. Needs are individualized, and it is best to get specific energy and protein needs from a dietician. If energy and protein needs are not met, vitamins and minerals will not be absorbable to their full potential, as the role of some vitamins is to aid in metabolism [58].

Fats: There are no recommended dietary allowances for lipids in cancer patients however, n-3 polyunsaturated fatty acids and eicosapentaenoic acid are reported to be beneficial in preventing weight loss and improve immunity. Anti-cancer effects of coconut oil have been reported in the literature, in chemically induced cancers of the colon and breast. Coconut oil is reported to be more protective than unsaturated oils [59,60].

### Vitamins

The need for vitamins and minerals is increased in this patient population. Oxidative stress and inflammation contribute to several organ toxicities, including neurotoxicities, after common cancer chemotherapy regimens. In addition to protein and energy malnutrition, patients with HNC may be at risk for vitamin and mineral deficiencies. As part of the nutritional management of these patients, it is important to replenish protein, energy, vitamin and mineral in the required amounts. It is important that patients notify their medical team of any medications and vitamin, mineral, or herbal supplements they may be taking [61]. Specific vitamins help with certain types of cancer. Fat soluble vitamins and vitamin B12 supplements should be used for people with gallbladder, bile duct and pancreas cancer because the absorption for those vitamins may be impaired. Liver cancer should be supplemented with fat-soluble vitamins and folic acid. Stomach cancer may cause people to have trouble absorbing fat; therefore the fat-soluble vitamins should be supplemented. Vitamin B12 may also be supplemented, as its absorption may be impaired [57].

### Nutrition Intervention

The process of nutrition assessment results in nutrition diagnosis. The nutrition diagnosis identifies the actual occurrence, the risk, or the potential for developing nutrition related problem. Nutritional intervention refers to the specific activities required to address and correct the nutrition diagnosis. It is designed, planned and implemented with the intent of improving the patient's nutrition status. Planning of the intervention requires the input of all disciplines [29]. Cancer and its treatment affects the nutritional status of patients by altering their metabolic function and reducing their food intake. Dietary modifications and supplements are used widely by patients with cancer and pre-invasive lesions as an adjunct to standard treatment. International guidelines on the nutritional management of patients with cancer recommend intervention with dietary advice and/or oral nutritional supplements in patients who are malnourished or those judged to be at nutritional risk, but the evidence for these recommendations is lacking. Nutritional intervention is significantly associated with improvements in energy intake and weight gain, some aspects of QoL but do not improve mortality. Nutritional intervention studies are limited in India.

### Commercial formulation

Commercial formulations for cancer are now available in India, which are enriched with eicosapentaenoic acid (EPA) and n-3 polyunsaturated fatty acid derived from fish oil. In a double blind, multi-centric randomized trial, 200 patients with pancreatic cancer were supplemented with a high protein, energy dense oral supplement enriched with EPA and a control supplement without EPA for eight weeks. On an intention-to-treat basis there was no difference between the controls and the EPA subjects, with both groups gaining weight. It was explained that, this was probably due to inadequate consumption of the supplement. Patients in this study only managed a mean 1.4 servings per day, while patients in the successful pilot study had managed 1.9 servings per day. When examined, the results from those who had consumed the recommended intake of 1.5-2.0 servings of the supplement per day for 8 weeks, it was found that they gained more weight (1.21 kg vs. 0.09 kg) and lean body mass (1.46 kg vs. 0.45 kg) than patients who were taking the oral supplement without EPA [62]. This commercial formulation for cancer, might have prevented weight loss but the key ingredient EPA being an animal source may not be acceptable by all subjects due to socio-cultural practices. Cancer patients with a vegetarian food pattern would not want to prefer a food formulation enriched with fish oil. Also, the high cost of the formulation will limit its use by the economically weaker patients.

### Need for low cost Cancer specific food formulation in India

In the present times, various commercial formulations are available for Cancer without regional specificity for different types or sites of cancer. A major limiting factor of the commercial tube feeding formulations in India is their cost. Therefore, their use is limited considering the economic scenario of Indian patients and can be used only as a supplement to the blenderized feed. In view of the rise in cancer prevalence in the recent decades and associated treatment induced malnutrition, there is an urgent need for low cost, clinically and metabolically effective food formulations.

In India, various studies have been conducted to assess the nutritional status of patients with different types of cancers [31,63-66] which showed a definitive risk of malnutrition in more than 80% of the patients. In a pilot study conducted in two cancer hospitals of Mysore city, India; to assess the nutritional status and needs of patients with HNC, it was found that malnutrition was prevalent among the subjects as reflected by somatic parameters (low BMI), Haemoglobin, total platelet count. Their nutrient intakes were deficit with respect to energy (28%), protein (25%), fat (45%) and carbohydrate (39%) and micronutrients intake did not meet the suggested daily intake [67]. Therefore, patients with HNC have the highest rate of malnutrition due to swallowing problems and effect of treatment.

### Alternative therapy

Researchers are now focusing on medicinal plants with anti-cancer properties and its use as nutraceuticals. Few commonly available Indian medicinal plants such as Tulasi (*Ocimum sanctum*) [68], Cinnamon (*Cinnamomum cassia*) [69], Custard apple (*Annona squamosa*) [70] and *Achyranthes aspera* Linn [71] are known to possess anti-cancer properties. These plants have proven promising effects in reducing tumor progression in animal and cell line models. Validation of their effect *in vivo* is needed.

### Conclusion

Cancer is a complex disease with cytokine-induced metabolic derangements. Patients with HNC have one of the highest malnutrition prevalence rates due to their inability to take food orally because of obstruction in the affected area with their diets deficit in most of the nutrients. Nutrition Impact Symptoms induced by oncological therapies such as Radiotherapy and Chemotherapy worsen the nutritional status affecting QoL and functional capacity. There is limited literature available on the impact of nutritional intervention in improving the nutritional status of patients with HNC due to its complex, multifactorial nature. In India, commercially available formulations are high in cost and are not disease specific; therefore there is a need to formulate a low cost food formulation using functional ingredients which could meet the nutritional needs and reduce the financial burden of cancer patients in India.

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