

## REVIEW ARTICLE



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## IAPEN INDIA Consensus Statement on Nutritional Management in Head and Neck Cancers

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## Abstract

Nutritional support is an integral component in the treatment of head and neck cancers (HNC). Studies indicate 90% of HNC patients are at high risk of developing malnutrition. Chemo-radiation and surgery, the three common treatments used to treat HNC are highly susceptible to toxic side effects. Dysphagia is often underestimated in HNC patients. A prolonged impaired swallowing process can lead to severe morbidities like malnutrition, dehydration, aspiration, pneumonia, and even death. These complications have adverse effects on patients' QoL (Quality of Life) and mental health. These

adverse reactions further complicate the nutritional status of the patients and the final treatment outcome, increasing morbidity and mortality. The consensus statements try to address nutritional issues and provide practical recommendations for practicing dietitians and clinicians.

**Keywords:** Head and neck cancer guidelines; Nutrition in head and neck cancers; Consensus statements in nutrition in Head and neck cancers; IAPEN head and neck cancer guidelines

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## Introduction

The prevalence of malnutrition in HNC patients is very common. Ninety percent of HNC patients are at risk of developing malnutrition during cancer treatment.<sup>(1)</sup> Malnutrition has a direct impact on a patient's ability to manage treatment and affects the QoL and survival. Patients often experience reduced food intake even before the diagnosis and continues throughout the treatment. As an alternative to feeding, patient's when oral feed is inadequate, enteral and/or parenteral nutrition emerges as an efficient tool for ensuring adequate nutrition. In certain HNC cases, prophylactic enteral feeding (nasogastric or gastrostomy feeding) showed some advantages in terms of progressive malnutrition (weight loss), hospital readmissions, and addressing dysphagia.<sup>(2)</sup> Several studies have proposed malnutrition as an independent risk factor, there is an urgent need for nutritional guidelines and the implementation of multi-disciplinary strategies to prevent and treat malnutrition in HNC patients during treatment and later during survivorship. A prolonged weight reduction and decline in nutritional status promote catabolism and chronic low-grade inflammation. This may lead to treatment complications and the cumulative impact that may be harmful and can be serious in nature characterized by loss of lean mass, compromised immunity, poor QoL, increased hospital stay, and mortality chances.<sup>(3)</sup>

## Methodology

A PubMed/Web of Science/EMBASE search for relevant papers, randomized clinical trials, systematic reviews, established guidelines, recommendations, and

consensus statements indexed in the literature from January 1, 2015, to September 30, 2022, was conducted. Relevant publications were selected for review based on clear criteria. Findings from the reviewed literature were merged and discussed in several rounds of deliberations from 15-10-2022 till 30-10-2022. As there was a dearth of Indian studies, the consensus statement committee has to rely on available international publications. Consensus statements were discussed and proposed after approval from the majority of committee members. It was accepted that the consensus statements will be called recommendations. In total, 27 experts including oncologists, nutritionists, and speech-swallowing therapists participated in the process of reviewing literature, deliberation, discussing, drafting, and approval of recommendations. Participants were informed to vote on the recommendation statements as "strong consensus", "moderate consensus" and "poor consensus". Finally, recommendations were graded as per the majority votes. The entire final draft including comments and recommendations was approved unanimously.

## Nutrition Screening and Assessment

For effective nutritional management nutritional screening should be performed at the time of diagnosis to identify at-risk patients or those who are already malnourished.<sup>(4)</sup> Nutritional support is recommended at all stages of the treatment for all HNC patients.<sup>(2)</sup> Hence, screening and nutritional assessment should be performed periodically throughout each phase of the treatment and during survivorship as well.

Screening can be done by any validated tool<sup>(5)</sup> Malnutrition Universal Screening Tool (MUST), Nutrition Risk Screening 2002 (NRS-2002) can be used specifically for inpatients.<sup>(3,6,7)</sup>

## Nutrition screening

Recommendation	Comment
To recognize nutritional disorders at the earliest and treat them effectively, all HNC patients should be screened at the time of diagnosis. Since nutritional status can change rapidly, screening should be repeated at regular intervals throughout the treatment.	Strong consensus

Malnutrition screening can identify early HNC patients with oral dysphagia and those who are at risk of malnutrition and may subsequently need to be referred to a dietician for a comprehensive assessment and nutrition intervention and monitoring.<sup>(7)</sup> Validated screening tools like Malnutrition Screening Tool (MST), Malnutrition Universal Screening Tool, and Nutrition Risk screening (NRS2002) can be used.<sup>(7)</sup>

## Nutrition assessment

Recommendation	Comment
All patients during screening found to be malnourished or at risk should undergo a comprehensive nutritional assessment by a qualified dietician within 24hrs or at the earliest possible time for effective nutritional intervention. Nutritional assessment should be repeated at regular intervals during the entire treatment and if possible during survivorship for better QoL and as a cancer recurrence preventive strategy.	Strong consensus

## Nutrition assessment tool

Recommendation	Comment
For nutritional assessment, the committee recommends the use of validated nutrition assessment tools like Subjective Global Assessment (SGA). Patient-Generated-Subjective Global Assessment (PG-SGA) can be used in a literate population to assess nutritional status.	Strong consensus

All those patients with nutritional risk should immediately undergo a comprehensive nutritional assessment. PG-SGA or SGA has been proven to be effective in cancer patients' nutritional assessment.<sup>(7)</sup> A detailed nutritional assessment

should be able to assess subjectively and objectively to quantify specific nutritional needs. Therefore, a comprehensive nutritional assessment should include anthropometric measurements, recent and past medical history, altered dietary intake, and physical examination along with evaluation of functional capacity and cognitive changes, medications, and laboratory investigations.<sup>(3)</sup>

## Nutrition assessment by imaging techniques

Recommendation	Comment
Imaging techniques/investigations like Bioelectrical Impedance Analysis (BIA), dual-energy x-ray absorptiometry (DEXA), computed tomography (CT), Magnetic resonance imaging(MRI), and ultrasound (USG) provide accurate information on lean mass and fat-free mass and even bone health. This provides a better perspective of their skeletal-muscle health for effective dietary recommendations accordingly. These resources are expensive but needs to be encouraged to help better nutritional assessment and treatment outcome.	Moderate consensus

Several imaging methods can precisely evaluate body muscle mass. Advanced techniques for body composition analysis such as BIA, DEXA, CT, MRI, and USG imaging are gold standards that appear to be the most accurate in measuring adipose tissue and organs in clinical practice.<sup>(8)</sup> Patients' performance status can be assessed by using the Eastern Cooperative Oncology Group (ECOG) scale that may help to identify patients, who may benefit from therapeutic and rehabilitative interventions.<sup>(4,9,10)</sup> Hand Grip Strength (HGS) by hand grip dynamometer can be a useful tool in measuring muscle strength.<sup>(4)</sup>

## Dysphagia screening and assessment

Recommendation	Comment
To maximize the nutritional intervention benefits, all HNC patients should have a pre-treatment baseline assessment of the swallowing capabilities of patients with dysphagia. The swallowing capability assessment should be repeated at regular intervals throughout the continuum of care.	Moderate consensus

Dysphagia is the most frequent and important symptom of HNC. Studies indicate approximately 50% of HNC patients present with oropharyngeal dysphagia.<sup>(11)</sup> Neuromuscular and sensory damage due to cancer treatment can affect swallowing capacity. Malnutrition, dehydration, even aspiration,

and pneumonia can be caused due to impaired swallowing ability. Tumor location and treatment modalities can predict swallowing disorders. Dysphagia screening at the baseline and periodical screening during the treatment can help in detecting high-risk patients. Timely and proper treatment selection, prophylactic exercises, and teaching and training of swallowing maneuvers can reduce impairments, and could optimize functional and therapeutic results, and improve QoL too. <sup>(12–15)</sup>

## Radiation and nutrition evaluation

Recommendation	Comment
All patients planned for chemo-radiation therapy to the head and neck region should be referred to the dietitian for nutrition evaluation and nutrition support.	Strong consensus

Radiation therapy to the head and neck area can cause several toxic effects that can make the patient difficult to consume adequate amounts of food and fluids. These side effects include loss of appetite, changes in taste, odynophagia, xerostomia, difficulty in chewing, denture issues, oral mucositis (OM), trismus, and dry mouth. Patients receiving radiation for HNC have increased nutritional requirements. Toxic effects of treatment may lead to weight loss. For a better treatment outcome, it is important that the patients maintain their weight to prevent treatment disruptions.

## Nutrition substrates

HNC patients may have difficulties in food consumption due to the location of the tumor causing eating, chewing, and swallowing a difficult and painful process. <sup>(16–18)</sup> Therefore, most HNC patients may have poor nutritional status before initiating the treatment, which influences negative prognosis and survivorship. <sup>(19,20)</sup> Thus, the nutrition goal for HNC patients is to maximize nutrition intake either orally or through nutrition support therapy when oral intake is inadequate. The primary aim is to preserve body weight, and muscle mass, prevent treatment interruptions and unplanned hospitalizations, and thereby improve treatment outcome and QoL. <sup>(21)</sup> Therefore, all HNC patients should receive intensive dietary counseling and adequate nutrient supplies throughout the treatment. <sup>(2)</sup>

## Energy requirements

Adequate feeding of cancer patients is of paramount importance to prevent malnutrition and its overall impact. TEE for a cancer patient can be calculated as a sum of the resting energy expenditure (REE), [which can be derived by indirect calorimetry], energy for physical activity, and, diet-induced

Recommendation	Comment
Total energy expenditure (TEE) of cancer patients, can be measured with predictive equations or it should be considered equal to healthy individuals depending upon performance status generally ranging between 25 and 30 kcal/kg/day. Indian population's physical structure and physical activities are heterogenic. Depending upon the prevailing body weight and desired body weight, to be achieved in near future, energy requirements can further be increased or decreased.	Moderate consensus

thermogenesis. <sup>(22)</sup> The TEE in cancer patients with reduced physical activities will be lower than in healthy individuals, while REE is increased in many cancer patients. <sup>(23–25)</sup> Various international societies after evaluating several studies have defined the energy requirements of a cancer patient to be equal to a healthy individual. <sup>(1,6,22,26)</sup>

## Protein requirements

Recommendation	Comment
To achieve a positive nitrogen balance, we suggest 1.2 to 1.5 g/kg BW/day. The protein requirements in patients with advanced hepatic encephalopathy, renal complications, or clinical conditions with varying protein requirements need to be assessed separately.	Strong consensus

Wasting of muscle mass is strongly related to poor functional capacity, treatment toxicity, and adverse outcome in cancer patients. <sup>(27)</sup> Protein synthesis in cancer patients is not impaired and it is responsive to higher consumption of protein. <sup>(28)</sup> HNC patients who undergo surgeries as a part of the treatments, perioperative morbidity, and poor wound healing are common. <sup>(29)</sup> HNC patients undergoing aggressive chemo-radiation, and having potential toxic effects impacting the treatment outcome should be identified for an aggressive nutrition regime. <sup>(6)</sup> Protein is required not just to build and maintain muscles, it has many other important physiological functions. Adequate provision of proteins can achieve positive nitrogen balance, faster recovery from toxic side effects of treatments, and help to build muscles or prevent muscle loss. <sup>(27)</sup> European society for nutrition and metabolism (ESPEN) <sup>(1)</sup>, Nutritional management in head and neck cancer: United Kingdom National Multidisciplinary Guidelines <sup>(30)</sup> Evidence-based practice guidelines for the nutritional management of adult patients with HNC, Cancer Council Australia. <sup>(6)</sup> recommend protein in the range between 1.2 to 1.5g/kg/day.

## Omega 3 fatty acids

Recommendation	Comment
Omega 3 Fatty Acid supplementation can be considered in weight-losing cancer patients, and patients affected by potential chemoradiation toxic effects during cancer treatment.	Moderate consensus

In a Randomized Control Trial (RCT), 37 ambulatory post-operative HNC patients showed improvement in blood protein concentration and lymphocyte levels after they consumed nutritional supplements enriched with omega-3 fatty acids<sup>(31)</sup> In a systematic review, five out of seven studies reported a beneficial effect of omega-3 enriched Immuno-nutrient formula on the nutritional status of HNC patients by reducing treatment toxic effects.<sup>(32)</sup> Studies strongly indicate that  $\omega$ 3 PUFA increases nutrient intake and has a significant role in improving increasing body weight and body composition in cancer patients.<sup>(33–39)</sup> Couple of studies have demonstrated the protective effect of omega-3 fatty acids on chemo-induced neuropathy.<sup>(38,40)</sup> Lyra et al in their meta-analysis, reported omega-3 ( $\omega$ -3) supplementation, with or without other immunonutrients, has benefited in maintaining or improving patients' body weight, BMI, and positive impact on nutritional status.<sup>(41)</sup> In post-operative conditions,  $\omega$ -3 PUFA supplementation has been shown to reduce inflammatory state<sup>(42)</sup>, infection incidents<sup>(43–45)</sup>, and improve overall survival<sup>(46)</sup> and QoL.<sup>(47)</sup> Hence,  $\omega$ -3 PUFA seems to have beneficial effects on various clinical conditions.

## Glutamine supplementation

Recommendation	Comment
We suggest the use of oral glutamine in HNC patients undergoing RT-CT with caution. The committee has no consensus statements on topical glutamine and parenteral glutamine recommendations in preventing or treating OM.	Moderate Consensus

A systematic review of twenty studies involving 1535 patients suggested supplementation with glutamine did not reduce the overall incidence of mucositis but delayed the onset of oral mucositis.<sup>(32)</sup> In another systematic review conducted by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer / International Society of Oral Oncology (MASCC/ISOO), out of 78 papers that were identified, 29 papers were analyzed. Some of these studies had heterogeneous patient populations with varying degrees of CTRT treatment. Based on the evidence level the committee stated in favor of oral glutamine with caution in HNC patients for the management of OM.<sup>(48)</sup> The meta-analysis of RCTs by Lyra et al has found significantly lower

mucositis grades and shorter mucositis duration in interventional groups compared to controls.<sup>(41)</sup> In an RCT of 144 patients with nasopharyngeal cancer, who had received concurrent chemoradiotherapy (CCRT) were administered parenteral glutamine. In the glutamine (+) group 90% of patients and in the glutamine (-ve) group 92% of patients developed all-grade OM.<sup>(49)</sup> A meta-analysis of RCTs concluded oral glutamine supplementation with no certain clinical benefits in the radiation-induced onset of OM, preventing or reducing incidence and severity in HNC patients.<sup>(50)</sup>

## Immunonutrition in mucositis

Recommendation	Comment
Due to insufficient evidence, we are not recommending immunonutrition supplementation in reducing mucositis incidence and its severity.	Moderate Consensus

## Immunonutrition in HNC surgeries

Recommendation	Comment
Due to inconsistent and insufficient evidence, we recommend the use of immunonutrition supplementation in HNC surgical patients either intravenous or enteral with caution.	Moderate Consensus

A systematic review of twenty studies indicated that immunonutrient-enriched formulas in HNC patients during chemo-radiation may have a positive impact on maintaining nutrition status.<sup>(32)</sup> In another review paper, Immunonutrition showed to reduce postoperative fistula formation, but there was no other positive outcome on length of hospital stay, wound infection, and adverse events.<sup>(51)</sup> In a systematic search of oral or enteral immunonutrition versus standard nutrition, Miller et al concluded that there is insufficient evidence on the beneficial effects of immunonutrition on infectious episodes in heterogeneous populations including HNC patients during chemotherapy.<sup>(52)</sup> In 96 HNC patients undergoing salvage surgery for squamous cell carcinoma, preoperative supplementation of immunonutrition showed improvements in tissue regeneration,<sup>(53)</sup> immune response,<sup>(53)</sup> reduced complication rates, and length of hospital stay.<sup>(53,54)</sup> In an RCT of 88 HNC patients receiving CCRT, immunonutrition supplementation in 45% of patients saw lower hematological toxicities and a much lower percentage of severe nonhematologic toxicities with no effect on the 2-year overall survival. However, the results were not statistically significant.<sup>(55)</sup> In 110 HNC patients undergoing definitive CCRT immunonutrition did not show any advantages in reducing the risk of mucositis.<sup>(56)</sup> A double-blind phase III



trial of immunomodulating nutrition formula administered during adjuvant chemoradiotherapy failed to reduce severe mucositis, but there was an improvement in the long-term survival and progression-free survival of compliant Head and Neck Squamous Cell Carcinoma (HNSCC) patients.<sup>(46)</sup> Further investigations and well-planned larger studies are needed, to clarify the definite benefits, timing, dosage, and duration of immunonutrition.

## Arginine

Recommendation	Comment
Due to inconsistent evidence, routine use of arginine supplementation cannot be recommended.	Moderate Consensus

The arginine-enriched formula showed to decrease in the incidence of fistulas in the HNC patient's post-surgery period with a reduction in the length of hospital stay. However, the advantages seemed to be statistically insignificant after adjusting for age, tumor stage, or aggressiveness of the surgery.<sup>(57)</sup> Similarly, in a meta-analysis, 397 patients from six studies receiving arginine as a single substance with other nutrition saw a reduction in fistulas (OR  $\frac{1}{4}$  0.36, 95% CI: 0.14 to 0.95,  $p$   $\frac{1}{4}$  0.039), and LOS (mean difference: 6.8 d, 95% CI: 12.6 to 0.9 d,  $p$   $\frac{1}{4}$  0.023). But, there was no benefit observed in wound infections or other infections.<sup>(58)</sup> Another RCT showed that enteral arginine supplementation had no advantage in postoperative nutritional status, surgery-induced immune suppression, or clinical outcome in severely malnourished HNC patients.<sup>(59)</sup> A review paper on the use of arginine on inflammatory markers concluded no benefit on inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha values (TNF- $\alpha$ ).<sup>(60)</sup>

## Micronutrient deficiencies

Recommendation	Comment
HNC patients are at risk of developing micronutrient deficiencies from the time of diagnosis and throughout the treatment. Therefore routine checkup of micronutrient deficiencies is recommended.	Strong consensus

## Micronutrient (Vitamins and minerals supplementation)

Few studies indicate potential associations between vitamin D and HNC, and supplementation of micronutrients has been proposed to prevent several cancers.<sup>(61–65)</sup> HNSCC

Recommendation	Comment
Micronutrient supplementation is recommended in established nutrient deficiencies in amounts approximately equal to the RDA.	Strong consensus

patients with severe vitamin D deficiency have shown reduced immune cell activities.<sup>(66,67)</sup> Vitamin D supplementation, in these patients showed a significant rise in natural killer cell's (NKC) cytotoxic activities. It is also proposed in the study that Vitamin D substitution as an adjuvant in immune therapies such as cetuximab and nivolumab treatment could support antitumorigenic activities, thus improving patients' prognosis.<sup>(66)</sup> Vitamin D/cisplatin combinations were seen to be effective in killing cisplatin-resistant cells.<sup>(68)</sup> Few studies have proposed vitamin D deficiency may increase the incidents and mortality of HNC.<sup>(69–73)</sup> Some studies have suggested that vitamin D supplementation in cancer patients could improve survival rates.<sup>(74)</sup> contrary to these studies Meyer F et al found no influence of pre-treatment vitamin D status on the disease outcome in HNC patients.<sup>(75)</sup> whereas some studies have asked for more RCTs in this area of research for a definite conclusion.<sup>(76)</sup>

The dietary assessment of 114 HNC patients through FFQs showed reduced micronutrient intake. The majority of HNC patients did not meet their recommended dietary intakes for vitamins D, E, C, folate, and magnesium.<sup>(77)</sup> The Netherlands Cohort Study which included 120,852 participants completed an FFQ that revealed a strong inverse association between vitamin C and overall HNC incidents.<sup>(78)</sup> In the same study, no statistically significant results were seen for other nutrients such as vitamin E,  $\alpha$ -carotene,  $\beta$ -carotene, lycopene, and lutein plus zeaxanthin.<sup>(78)</sup> A prospective RCT of 62 HNC patients who underwent surgery, reported a deficiency of protein, vitamin D, zinc, and iron immediately after surgery.<sup>(79)</sup> In 29 HNSCC patients, the blood samples collected after radiotherapy, plasma lutein, zeaxanthin,  $\alpha$ -carotene,  $\beta$ -carotene, lycopene, and total carotenoids were found to be significantly lower.<sup>(80)</sup>

## Vitamin E as a therapeutic intervention in treating mucositis

Recommendation	Comment
Vitamin E applicant is recommended with caution in preventing or treating OM.	Moderate consensus

## Vitamin A as a therapeutic intervention in treating mucositis

Recommendation	Comment
There is insufficient evidence to recommend vitamin A applicants in treating or preventing OM.	Moderate consensus

OM is one of the most common toxic effects seen in HNC patients undergoing anticancer therapies. A survey of scientific literature published between the years 2004 and 2019 revealed a positive effect of vitamin E, zinc, and glutamine in preventing and treating OM.<sup>(81)</sup> A systematic analysis revealed that Vitamin E topical application had performed better on OM than Vitamin E systemic administration. Vitamin A topical treatment also showed a reduction in the severity of OM similar to vitamin E.<sup>(82)</sup>

## Zinc

Recommendation	Comment
There's inconsistent evidence of the benefits of zinc supplementation in addressing mucositis, taste, and dermatitis, we cannot recommend routine use of zinc supplements in treating or preventing OM, dermatitis, and/or improving taste.	Moderate consensus

Zinc is a trace element that has an important role to play in immunity and cell growth.<sup>(9)</sup> The serum zinc level was seen to have an inverse relation with the early development of mucositis and dermatitis.<sup>(83)</sup> Zinc has been proposed to have a therapeutic impact on taste loss and OM.<sup>(84,85)</sup> A systematic review by C Hoppe et al concluded that Zinc supplementation can prevent oral toxicities, and dermatitis during radiation but no improvement in mucositis or other side effects induced by chemotherapy.<sup>(84)</sup> In a meta-analysis, three studies favored zinc in reducing the incidence and severity of mucositis in HNC patients undergoing radiotherapy with or without chemotherapy and one study by Gorge et al found no benefits in the incidence of mucositis.<sup>(86)</sup> In an RCT of 120 HNC patients, 60 patients, received 150mg of Zinc sulfate once daily benefited in the delay of onset, decrease in severity, and duration of oropharyngeal mucositis.<sup>(87)</sup> In a retrospective study 202 HNC patients, out of which 95 patients received Zinc supplementation and fared better in salivary gland toxicities compared to the others who did not receive Zinc supplements.<sup>(88)</sup> In a systemic review of four RCTs involving 162 HNC patients, zinc sulfate supplementation did not find the benefit of prophylaxis against radiation-induced OM.<sup>(89)</sup>

Similarly, another review of five RCTs of oral zinc sulfate found no clinical benefits in chemotherapy-induced OM in preventing or reducing the incidence, severity, or pain intensity.<sup>(90)</sup>

In a review of twelve RCTs majority of studies showed the benefits of glutamine and zinc supplementation in delaying the onset of OM and reducing the severity in HNC patients receiving chemoradiotherapy.<sup>(91)</sup>

## Perioperative nutrition

Perioperative nutrition deals with preoperative, intraoperative, and postoperative care. Perioperative nutrition plays a vital role in patients with poor nutritional status and surgical outcomes. Perioperative nutrition includes prehabilitation, preoperative carbohydrate loading, and immunonutrition.<sup>(92)</sup>

## ERAS feasibility and benefits in HNC surgeries

Recommendation	Comment
HNC patients may benefit from the implementation of comprehensive ERAS protocols, as ERAS can expedite their recovery, food intake, pain, speech, swallowing, and communication.	Strong consensus

Perioperative nutritional support, as recommended within the ERAS (Enhanced Recovery After Surgery) protocol, has been shown to be beneficial in achieving better results postoperatively.<sup>(93,94)</sup> ERAS is an earnest attempt to use metabolic strategy to reduce perioperative stress, reduce post-operative complications, reduce hospital stay, and thus improve post-operative outcomes.<sup>(94–96)</sup> A significantly shorter LOS was observed in the ERAS group of patients (median, 14 days; range, 10–19) compared to the non-ERAS group (median, 17.5 days; range, 13–21) ( $p = 0.0128$ ).<sup>(97)</sup> In a recent study, Twenty-five patients underwent surgery with ERAS protocols with perioperative nutrition supplementation. A strong negative correlation between the modified Nutrition-Related Index (mNRI) and the number of complications ( $P = 0.01$ ), specifically, fistula rate ( $P = 0.04$ ) and unplanned reoperation ( $P = 0.04$ ) was observed.<sup>(94)</sup> HNC patients can benefit from comprehensive ERAS protocols, by helping them enhance their recovery, including breathing, food intake, pain, speech, swallowing, and communication.<sup>(98)</sup> Prolonged inadequate oral intake is associated with higher mortality.

## Perioperative nutrition

Prehabilitation or preoperative nutritional management does not mean correcting years of nutritional deficiencies. It focuses on optimizing the malnourished or at-risk patients for surgical stress which are complex and diverse.<sup>(99)</sup>

Recommendation	Comment
Pre-operative nutrition buildup of 10-14 days is recommended, specifically in malnourished or at-risk patients undergoing major surgery, even if the surgery has to be delayed.	Strong consensus

Nutrition support of 10-14 days is recommended in severely malnourished or at-risk patients before major surgery even if surgery has to be delayed.<sup>(30)</sup> Perioperative nutritional optimization by carbohydrate loading consistent with ERAS recommendations is safe and well tolerated in patients undergoing head and neck surgery.<sup>(30,100)</sup>

### Perioperative immunonutrition

Recommendation	Comment
Pre operative immunonutrition has shown no additional benefits like reduced infections or faster wound healing compared to standard nutrition. However, post-operative immunonutrition may be considered with caution to benefit from reduced length of stay and reduced fistula formation.	Moderate consensus

In HNC surgeries preoperative immunonutrition studies have not shown any additional benefits compared to standard nutrition support in patients undergoing HNC surgery. Investigations have produced mixed results in this population. There are large variations in the study designs, the composition of immunonutrition formulas, administration protocols, and the period of administration.<sup>(101,102)</sup> In a non-randomized study of 195 high-risk HNC patients undergoing surgery, 59% of the patients were prescribed arginine enriched nutritional supplements, and 41% did not. Of those who did not receive the supplement, 38 (47.5%) patients experienced postoperative complications compared to 29 (25.2%) patients who consumed the arginine enriched supplement ( $p=0.0021$ ). On average 2.8 days longer hospital stay was observed in patients who did not have enhanced nutrition ( $p=0.02$ ), and there was no difference in readmission rates between the two groups ( $p=0.91$ ).<sup>(103)</sup> Similar results were observed in a retrospective study in patients who received immunonutrition had a lower fistula occurrence rate (17.91% vs. 32.84%;  $p=0.047$ ) and a shorter mean Length of Stay (LOS) [28.25 (SD 16.11) Vs 35.50 (SD 25.73) days;  $p=0.030$ ].<sup>(57)</sup> In a systemic review of 19 RCTs (1099 patients) the authors found no evidence of a difference in the LOS (mean difference -2.5 days, 95% confidence interval (CI) -5.11 to 0.12). Similarly, the effect of immunonutrition on wound infection was found to be poor (risk ratio (RR) 0.94, 95% CI 0.70 to 1.26) However, there was reduced fistula formation with immunonu-

trition group; the absolute risks were 11.3% and 5.4% in the standard care and immunonutrition groups, with a RR of 0.48 (95% CI 0.27 to 0.85). But the study concluded that the evidence was of low quality.<sup>(51)</sup> A review article of 19 studies with 1099 HNC patients found no benefit of immunonutrition on wound infection.<sup>(51)</sup>

### Pre-operative carbohydrate loading

Recommendation	Comment
Consider carbohydrate loading in patients undergoing head and neck surgeries and use cautiously in diabetic patients considering glycemic variability.	Moderate consensus

The rationale for preoperative carbohydrate loading is that a fed state before surgery can attenuate insulin resistance and catabolism, improves better glucose management, and preserves lean body mass.<sup>(104)</sup> A large number of studies on the role of carbohydrate loading in HNC surgeries are limited. However, the studies strongly indicate carbohydrate loading in patients undergoing HNC surgeries is safe and well tolerated.<sup>(97)</sup>

### Route of feeding

Recommendation	Comment
The oral route with counseling is the preferred choice to improve nutrition and nutritional supplements should be recommended if counseling is not effective. In conditions when oral feeding is not possible or intake is less than 60% of daily requirements and the condition is going to prevail for the next five days or more enteral tube feeding can be considered. In case of a nonfunctional gut expected for more than five days, TPN can be started.	Strong consensus

The intestine; other than the digestive, absorptive, and endocrine processes, also has an effective immunological function. The gut-associated lymphoid tissue (GALT) plays an important role in gut immunity as it is the host for many immune cells like B and T lymphocytes, macrophages, antigen-presenting cells, and enteroendocrine cells.<sup>(105,106)</sup> Mucosal starvation leads to lymphoid tissue atrophy, a decline in immune system function, and increased bacterial translocation.<sup>(107)</sup> SCCM-ASPEN critical care nutrition guidelines recommend the oral route as the preferred choice and encourage early enteral feeding when oral feeding is not an option available. If unable to meet 60% of caloric requirements through enteral feeds for several days, parenteral nutrition can be added.<sup>(30,108)</sup> High-risk patients or severely malnourished patients whose gut is not available for enteral feeding



should be administered TPN.<sup>(7,30,108)</sup> National Institute for Health and Care Excellence guidelines recommend gastrostomy feeding if enteral feeding is expected to prolong for more than four weeks.<sup>(109)</sup>

## Post-operatively when to start feeding

Recommendation	Comment
Feeding should start within 24 hours after the surgery. If oral feeding is not possible enteral feeding should be considered	Strong consensus

One of the principles of ERAS is the early initiation of oral or enteral tube feeding after all surgeries. Early initiation enteral feeding has been shown to reduce the risk of infection, improved insulin resistance, and reduced the number of hospital stays.<sup>(96)</sup> Early feeding increases gastrointestinal (GI) hormone secretion and improves macrophagic activity and increases intestinal absorptive function.<sup>(110)</sup> Studies in HNC surgeries have demonstrated that early feeding (oral diet) on POD-1 reduces the length of stay without increasing perioperative complications.<sup>(111)</sup>

## Diagnosis of Chyle's leak

Recommendation	Comment
Confirm chyle leak by analysis of drainage fluid for triglycerides and chylomicrons.	Strong consensus

## Nutritional management of Chyle's leak

Recommendation	Comment
For most patients with high-output postoperative chyle leaks, the preferred approach is early intervention (surgical/interventional radiology) rather than prolonged conservative therapy with nutritional modification. While awaiting surgery, the patients may be treated with tube thoracostomy drainage, bowel rest, and administration of TPN and somatostatin analogs. For most patients with low-volume postoperative chyle leaks or patients with chylothorax for nonsurgical reasons, an initial conservative approach is justified. The conservative management may include tube thoracostomy drainage, a low-fat diet, and administration of TPN and somatostatin analogs.	Strong consensus

Chyle leak (CL) leads to the loss of protein, fat, and fat-soluble vitamins, trace elements, and lymphocytes through the chyle. Large volume chyle loss may result in hypovolemia,

electrolyte imbalances, malnutrition, and immunosuppression<sup>(112–115)</sup>. CL can be confirmed by analysis of drained fluid for triglycerides and chylomicrons.<sup>(30)</sup> All suspected CL patients should be recommended to a conservative nonfat diet, low-fat diet, or medium-chain triglycerides (MCT) diet with bed rest and bed elevation.<sup>(109)</sup> Patients on a fat-free diet or diet with MCT for a prolonged period may need essential fatty acid supplements and fat-soluble vitamins. If CL does not resolve after fat restriction or the MCT diet does not respond satisfactorily to conservative management alone, and the drainage volume is consistently high, TPN can be administered.<sup>(109)</sup> Management of chylothorax depends on the etiology and whether the leak has a high (> 1 litre) or low (< 1 liter) output. There are multiple options for patients who fail to respond to the conservative measures, which include pleurodesis, percutaneous thoracic duct embolization/ disruption, or thoracic duct ligation.

## Nutrition in palliative care

Recommendation	Comment
The goals of nutrition in palliative care and at the end of life should be to improve QoL and symptom management. It is important to address issues of food and feeding rather than nutrients. Minimize food-related discomforts. Consider ethical questions before administering artificial feeding therapies.	Moderate Consensus

Advanced cancer patients' life expectancy may range from months to years. The main issues of cancer patients with chronic or incurable illnesses are cachexia and nutrition management. Palliative care should be focused on alleviating symptoms and improving QoL.<sup>(22,116)</sup> Attempts can be made for good nutritional status, physical activities, and psychosocial needs for palliative patients depending upon the expected survival period and performance status.<sup>(117)</sup> Patients at the end of life receiving palliative care experience difficulties in food intake.<sup>(116,117)</sup> Sánchez-Sánchez E et al, in their review concluded that even though the use of EN reduced diarrheal episodes and improved hospital survival, it increased visits to the emergency department and EN showed no benefit on the level of comfort and satisfaction over the group of patients those who were not on EN.<sup>(118)</sup> In a single-centered one-month observational study, 72 palliative care patients of which 34 (47%) were on parenteral nutrition had frequent venous access complications, edema, and poor QoL.<sup>(116)</sup> Thus the benefit of artificial nutrition in end-of-life treatment seems questionable and can lead to ethical issues. Artificial nutrition should be used with realistic goals of treatment outcome and wishes of patient and assessment by the doctor and other health care professionals.<sup>(118,119)</sup>

## Modified diet for patients with dysphagia

Dysphagia can lead to serious clinical conditions like malnutrition, dehydration, aspiration pneumonia, reduced functional capacity, and even death.<sup>(120)</sup> More than 50% of oropharyngeal cancer patients and patients who had undergone total glossectomy develop dysphagia.<sup>(11)</sup> Dysphagia has varied symptoms. The swallowing capacity of a patient with dysphagia should be evaluated by a speech and swallowing therapist.<sup>(121)</sup> The swallowing therapist based on the diagnosis will advise on the right texture of the food to ensure that they receive adequate nutrients. The bolus food consistency modification is an effective strategy for improving nutritional and hydration status in patients with dysphagia. In cases of severe dysphagia, patients will need enteral tube feedings.<sup>(120,121)</sup> The expert committee recommends the changes in the food textures as specified in Figure 1.







Modified textured dysphagia diet for Indians			
Water, coconut water, clear fruit juice, clear dal water, rice kanji, clear vegetable stalk, diluted milk, very thin buttermilk	Very thin		
Milk shakes, pulpy fruit juice, dal soup, lassi, buttermilk, thick vegetable stalk, shorba	Thick		
Nachni satva, thick porridge, cereal-pulse gruel, tomato soup, rava kheer,	Very thick		
Pureed khichdi, pureed vegetable, dalia, liquid upma, all pureed preparations	Pureed		
Khichdi, soft dal rice, curd rice, mashed potato/vegetables/pulses, kheema, bhurji, dalia,	Soft : minced		
Normal overcooked food, which can be easily softened by fingers before eating or very easy to chew	Overcooked		

Fig 1. Modified texture dysphagia diet chart

## References

- Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. *Clinical Nutrition*. 2017;36(5):1187–1196. Available from: <https://doi.org/10.1016/j.clnu.2017.06.017>.
- Wagner C. Nutritional management during treatment for head and neck cancer. *memo - Magazine of European Medical Oncology*. 2020;13(4):405–408. Available from: <https://doi.org/10.1007/s12254-020-00613-0>.
- Reber E, Gomes F, Vasiloglou MF, Schuetz P, Stanga Z. Nutritional Risk Screening and Assessment. *Journal of Clinical Medicine*. 2019;8(7):1–19. Available from: <https://doi.org/10.3390/jcm8071065>.
- Arends J, Bertz H, Bischoff S, Fietkau R, Herrmann H, Holm E, et al. S3-Leitlinie der Deutschen Gesellschaft für Ernährungsmedizin e. V. (DGEM) in Kooperation mit der Deutschen Gesellschaft für Hämatologie und Onkologie e. V. (DGHO), der Arbeitsgemeinschaft „Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin“ der Deutschen Krebsgesellschaft (ASORS) und der Österreichischen Arbeitsgemeinschaft für klinische Ernährung (AKE). *Aktuelle Ernährungsmedizin*. 2015;40(05):e1–e74. Available from: <https://doi.org/10.1055/s-0035-1552741>.
- Sandmæl JA, Sand K, Bye A, Solheim TS, Oldervoll L, sofie S Helvik A. Nutritional experiences in head and neck cancer patients. *European Journal of Cancer Care*. 2019;28(6). Available from: <https://doi.org/10.1111/ecc.13168>.
- Head and Neck Guideline Steering Committee. Evidence-based practice guidelines for the nutritional management of adult patients with

- head and neck cancer. Sydney: Clinical Oncological Society of Australia. 2022. Available from: [https://wiki.cancer.org.au/australia/COSA:Head\\_and\\_neck\\_cancer\\_nutrition\\_guidelines](https://wiki.cancer.org.au/australia/COSA:Head_and_neck_cancer_nutrition_guidelines).
- Kreymann KG, Berger MM, Deutz NEP, Hiesmayr M, Joliet P, Kazandjiev G, et al. ESPEN Guidelines on Enteral Nutrition: Intensive care. *Clinical Nutrition*. 2006;25(2):210–223. Available from: <https://doi.org/10.1016/j.clnu.2006.01.021>.
- Prado CM, Elliott SA, Mota JF. Advanced imaging techniques for assessment of undernutrition. *Advanced Nutrition and Dietetics in Nutrition Support*. 2018;p. 91–105. Available from: <https://doi.org/10.1002/9781118993880.ch2.7>.
- Wang JR, Habbous S, Espin-Garcia O, Chen D, Huang SH, Simpson C, et al. Comorbidity and performance status as independent prognostic factors in patients with head and neck squamous cell carcinoma. *Head & Neck*. 2016;38(5):736–742. Available from: <https://doi.org/10.1002/hed.23947>.
- Corrêa GTB, Bandeira GA, Cavalcanti BG, Santos FBG, Neto JFR, Guimarães ALS, et al. Analysis of ECOG performance status in head and neck squamous cell carcinoma patients: association with sociodemographical and clinical factors, and overall survival. *Supportive Care in Cancer*. 2012;20(11):2679–2685. Available from: <https://doi.org/10.1007/s00520-012-1386-y>.
- García-Peris P, Parón L, Velasco C, Cuerda CDL, Cambor M, Bretón I, et al. Long-term prevalence of oropharyngeal dysphagia in head and neck cancer patients: Impact on quality of life. *Clinical Nutrition*. 2007;26(6):710–717. Available from: <https://doi.org/10.1016/j.clnu.2007.08.006>.
- Christianen MEMC, Schilstra C, Beetz I, Muijs CT, Chouvalova O, Burlage FR, et al. Predictive modelling for swallowing dysfunction after primary (chemo)radiation: Results of a prospective observational study. *Radiotherapy and Oncology*. 2012;105(1):107–114. Available from: <https://doi.org/10.1016/j.radonc.2011.08.009>.
- Eisbruch A, Kim HM, Feng FY, Lyden TH, Haxer MJ, Feng MY, et al. Chemo-IMRT of Oropharyngeal Cancer Aiming to Reduce Dysphagia: Swallowing Organs Late Complication Probabilities and Dosimetric Correlates. *International Journal of Radiation Oncology\*Biophysics*. 2011;81(3):e93–e99. Available from: <https://doi.org/10.1016/j.ijrobp.2010.12.067>.
- Denaro N, Merlano MC, Russi EG. Dysphagia in Head and Neck Cancer Patients: Pretreatment Evaluation, Predictive Factors, and Assessment during Radio-Chemotherapy, Recommendations. *Clinical and Experimental Otorhinolaryngology*. 2013;6(3):117–126. Available from: <https://doi.org/10.3342/ceo.2013.6.3.117>.
- Clarke P, Radford K, Coffey M, Stewart M. Speech and swallow rehabilitation in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *The Journal of Laryngology & Otology*. 2016;130(S2):S176–S180. Available from: <https://doi.org/10.1017/s0022215116000608>.
- Larsson M, Hedelin B, Johansson I, Athlin E. Eating Problems and Weight Loss for Patients With Head and Neck Cancer. *Cancer Nursing*. 2005;28(6):425–435. Available from: <https://doi.org/10.1097/00002820-200511000-00004>.
- Langius JAE, Zandbergen MC, Eerenstein SEJ, Van Tulder MW, Leemans CR, Kramer MHH, et al. Effect of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving (chemo)radiotherapy: a systematic review. *Clinical Nutrition*. 2013;32(5):671–678. Available from: <https://doi.org/10.1016/j.clnu.2013.06.012>.
- Nugent B, Lewis S, O'Sullivan JM. Enteral feeding methods for nutritional management in patients with head and neck cancers being treated with radiotherapy and/or chemotherapy. *Cochrane Database of Systematic Reviews*. 2013. Available from: <https://doi.org/10.1002/14651858.cd007904.pub3>.
- Bhattacharjee A, Bahar I, Saikia A. Nutritional assessment of patients with head and neck cancer in North-East India and dietary intervention. *Indian Journal of Palliative Care*. 2015;21(3):289–289. Available from: <https://doi.org/10.4103/0973-1075.164889>.

- 20) Chasen MR, Bhargava R. A descriptive review of the factors contributing to nutritional compromise in patients with head and neck cancer. *Supportive Care in Cancer*. 2009;17(11):1345–1351. Available from: <https://doi.org/10.1007/s00520-009-0684-5>.
- 21) Ackerman D, Laszlo M, Provisor A, Yu A. Nutrition Management for the Head and Neck Cancer Patient. *Cancer Treat Res*. 2018;174:187–208. Available from: [https://doi.org/10.1007/978-3-319-65421-8\\_11](https://doi.org/10.1007/978-3-319-65421-8_11).
- 22) Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, et al. ESPEN practical guideline: Clinical Nutrition in cancer. *Clinical Nutrition*. 2021;40(5):2898–2913. Available from: <https://doi.org/10.1016/j.clnu.2021.02.005>.
- 23) Avancini A, Pala V, Trestini I, Tregnago D, Mariani L, Sieri S, et al. Exercise Levels and Preferences in Cancer Patients: A Cross-Sectional Study. *International Journal of Environmental Research and Public Health*. 2020;17(15):5351. Available from: <https://doi.org/10.3390/ijerph17155351>.
- 24) Gibney E, Elia M, Jebb S, Murgatroyd P, Jennings G. Total energy expenditure in patients with small-cell lung cancer: Results of a validated study using the bicarbonate-urea method. *Metabolism*. 1997;46(12):90140–90142. Available from: [https://doi.org/10.1016/s0026-0495\(97\)90140-2](https://doi.org/10.1016/s0026-0495(97)90140-2).
- 25) Moses AWG, Slater C, Preston T, Barber MD, Fearon KCH. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. *British Journal of Cancer*. 2004;90(5):996–1002. Available from: <https://doi.org/10.1038/sj.bjc.6601620>.
- 26) Peñas RDL, Majem M, Perez-Altozano J, Virizuela JA, Cancer E, Diz P, et al. SEOM clinical guidelines on nutrition in cancer patients (2018). *Clinical and Translational Oncology*. 2019;21(1):87–93. Available from: <https://doi.org/10.1007/s12094-018-02009-3>.
- 27) Ravasco P. Nutrition in Cancer Patients. *Journal of Clinical Medicine*. 2019;8(8):1211. Available from: <https://doi.org/10.3390/jcm8081211>.
- 28) Macdonald AJ, Johns N, Stephens N, Greig C, Ross JA, Small AC, et al. Habitual Myofibrillar Protein Synthesis Is Normal in Patients with Upper GI Cancer Cachexia. *Clinical Cancer Research*. 2015;21(7):1734–1740. Available from: <https://doi.org/10.1158/1078-0432.ccr-14-2004>.
- 29) Neseimeier R, Dunlap N, Mcclave SA, Tennant P. Evidence-Based Support for Nutrition Therapy in Head and Neck Cancer. *Current Surgery Reports*. 2017;5(8):18. Available from: <https://doi.org/10.1007/s40137-017-0179-0>.
- 30) Talwar B, Donnelly R, Skelly R, Donaldson M. Nutritional management in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *The Journal of Laryngology & Otolaryngology*. 2016;130(S2):S32–S40. Available from: <https://doi.org/10.1017/s002225116000402>.
- 31) De Luis DA, Izaola O, Cuellar L, Terroba MC, Fuente BDL, Cabezas G. A randomized clinical trial with two doses of a omega 3 fatty acids oral and arginine enhanced formula in clinical and biochemical parameters of head and neck cancer ambulatory patients. *Eur Rev Med Pharmacol Sci*. 2017;17(8):1090–1094. Available from: <https://pubmed.ncbi.nlm.nih.gov/23661523/>.
- 32) Tan SE, Satar NFA, Majid HA. Effects of Immunonutrition in Head and Neck Cancer Patients Undergoing Cancer Treatment – A Systematic Review. *Frontiers in Nutrition*. 2022;9(821924). Available from: <https://doi.org/10.3389/fnut.2022.821924>.
- 33) Burns CP, Halabi S, Clamon G, Kaplan E, Hohl RJ, Atkins JN, et al. Phase II study of high-dose fish oil capsules for patients with cancer-related cachexia. *Cancer*. 2004;101(2):370–378. Available from: <https://doi.org/10.1002/cncr.20362>.
- 34) Tobberup R, Carus A, Rasmussen HH, Falkmer UG, Jorgensen MG, Schmidt EB, et al. Feasibility of a multimodal intervention on malnutrition in patients with lung cancer during primary anti-neoplastic treatment. *Clinical Nutrition*. 2021;40(2):525–533. Available from: <https://doi.org/10.1016/j.clnu.2020.05.050>.
- 35) Patursson P, Möller G, Muhic A, Andersen JR. N-3 fatty acid EPA supplementation in cancer patients receiving abdominal radiotherapy - A randomised controlled trial. *Clinical Nutrition ESPEN*. 2021;43:130–136. Available from: <https://doi.org/10.1016/j.clnesp.2021.03.001>.
- 36) Fietkau R, Lewitzki V, Kuhnt T, Hölscher T, Hess NF, Berger B, et al. A disease-specific enteral nutrition formula improves nutritional status and functional performance in patients with head and neck and esophageal cancer undergoing chemoradiotherapy: Results of a randomized, controlled, multicenter trial. *Cancer*. 2013;119(18):3343–3353. Available from: <https://doi.org/10.1002/cncr.28197>.
- 37) Cereda E, Cappello S, Colombo S, Klersy C, Imarisio I, Turri A, et al. Nutritional counseling with or without systematic use of oral nutritional supplements in head and neck cancer patients undergoing radiotherapy. *Radiotherapy and Oncology*. 2018;126(1):81–88. Available from: <https://doi.org/10.1016/j.radonc.2017.10.015>.
- 38) Sánchez-Lara K, Turcott JG, Juárez-Hernández E, Nuñez-Valencia C, Villanueva G, Guevara P, et al. Effects of an oral nutritional supplement containing eicosapentaenoic acid on nutritional and clinical outcomes in patients with advanced non-small cell lung cancer: Randomised trial. *Clinical Nutrition*. 2014;33(6):1017–1023. Available from: <https://doi.org/10.1016/j.clnu.2014.03.006>.
- 39) Mcglory C, Calder PC, Nunes EA. The Influence of Omega-3 Fatty Acids on Skeletal Muscle Protein Turnover in Health, Disease, and Disease. *Frontiers in Nutrition*. 2019;6. Available from: <https://doi.org/10.3389/fnut.2019.00144>.
- 40) Ghoreishi Z, Esfahani A, Djazayeri A, Djalali M, Golestan B, Ayromlou H, et al. Omega-3 fatty acids are protective against paclitaxel-induced peripheral neuropathy: A randomized double-blind placebo controlled trial. *BMC Cancer*. 2012;12(1):12. Available from: <https://doi.org/10.1186/1471-2407-12-355>.
- 41) Lyra MDMF, De Meira JEC, Guedes GDS, Bueno NB. Immunonutrition in head and neck cancer: Systematic review and metanalysis of its clinical and nutritional effects. *Clinical Nutrition ESPEN*. 2021;41:30–41. Available from: <https://doi.org/10.1016/j.clnesp.2020.12.014>.
- 42) Machon C, Thezenas S, Dupuy AMM, Assenat E, Michel F, Mas E, et al. Immunonutrition before and during radiochemotherapy: improvement of inflammatory parameters in head and neck cancer patients. *Supportive Care in Cancer*. 2012;20(12):3129–3135. Available from: <https://doi.org/10.1007/s00520-012-1444-5>.
- 43) Boisselier P, Kaminsky MCC, Thézenas S, Gallocher O, Lavau-Denes S, Garcia-Ramirez M, et al. A double-blind phase III trial of immunomodulating nutritional formula during adjuvant chemoradiotherapy in head and neck cancer patients: IMPATOX. *The American Journal of Clinical Nutrition*. 2020;112(6):1523–1531. Available from: <https://doi.org/10.1093/ajcn/nqaa227>.
- 44) Aida T, Furukawa K, Suzuki D, Shimizu H, Yoshidome H, Ohtsuka M, et al. Preoperative immunonutrition decreases postoperative complications by modulating prostaglandin E2 production and T-cell differentiation in patients undergoing pancreatoduodenectomy. *Surgery*. 2014;155(1):124–133. Available from: <https://doi.org/10.1016/j.surg.2013.05.040>.
- 45) Uno H, Furukawa K, Suzuki D, Shimizu H, Ohtsuka M, Kato A, et al. Immunonutrition suppresses acute inflammatory responses through modulation of resolvins E1 in patients undergoing major hepatobiliary resection. *Surgery*. 2016;160(1):228–236. Available from: <https://doi.org/10.1016/j.surg.2016.01.019>.
- 46) Boisselier P, Kaminsky MCC, Thézenas S, Gallocher O, Lavau-Denes S, Garcia-Ramirez M, et al. A double-blind phase III trial of immunomodulating nutritional formula during adjuvant chemoradiotherapy in head and neck cancer patients: IMPATOX. *The American Journal of Clinical Nutrition*. 2020;112(6):1523–1531. Available from: <https://doi.org/10.1093/ajcn/nqaa227>.
- 47) Wei L, Wu Z, Chen YQ. Multi-targeted therapy of cancer by omega-3 fatty acids-an update. *Cancer Letters*. 2022;526:193–204. Available from: <https://doi.org/10.1016/j.canlet.2021.11.023>.



- 48) Yarom N, Hovan A, Bossi P, Ariyawardana A, Jensen SB, Gobbo M, et al. Systematic review of natural and miscellaneous agents for the management of oral mucositis in cancer patients and clinical practice guidelines—part 1: vitamins, minerals, and nutritional supplements. *Supportive Care in Cancer*. 2019;27(10):3997–4010. Available from: <https://doi.org/10.1007/s00520-019-04887-x>.
- 49) Wang CCC, Hwang TZZ, Yang CCC, Lien CF, Wang CCC, Shih YC, et al. Impact of Parenteral Glutamine Supplement on Oncologic Outcomes in Patients with Nasopharyngeal Cancer Treated with Concurrent Chemoradiotherapy. *Nutrients*. 2022;14(5):997. Available from: <https://doi.org/10.3390/nu14050997>.
- 50) Shuai T, Tian X, Xu LL, Chen WQ, Pi YP, Zhang L, et al. Oral Glutamine May Have No Clinical Benefits to Prevent Radiation-Induced Oral Mucositis in Adult Patients With Head and Neck Cancer: A Meta-Analysis of Randomized Controlled Trials. *Frontiers in Nutrition*. 2020;7(49). Available from: <https://doi.org/10.3389/fnut.2020.00049>.
- 51) Howes N, Atkinson C, Thomas S, Lewis SJ. Immunonutrition for patients undergoing surgery for head and neck cancer. *Cochrane Database Syst Rev*. 2018;8(8):CD010954. Available from: <https://doi.org/10.1002/14651858.cd010954.pub2>.
- 52) Miller LJ, Douglas C, McCullough FS, Stanworth SJ, Calder PC. Impact of enteral immunonutrition on infectious complications and immune and inflammatory markers in cancer patients undergoing chemotherapy: A systematic review of randomised controlled trials. *Clinical Nutrition*. 2022;41(10):2135–2146. Available from: <https://doi.org/10.1016/j.clnu.2022.07.039>.
- 53) Mueller SA, Mayer C, Bojaxhiu B, Aeberhard C, Schuetz P, Stanga Z, et al. Effect of preoperative immunonutrition on complications after salvage surgery in head and neck cancer. *J Otolaryngol Head Neck Surg*. 2019;48(1). Available from: <https://doi.org/10.1186/s40463-019-0345-8>.
- 54) Aeberhard C, Mayer C, Meyer S, Mueller SA, Schuetz P, Stanga Z, et al. Effect of preoperative immunonutrition on postoperative short-term outcomes of patients with head and neck squamous cell carcinoma. *Head Neck*. 2018;40(5):1057–1067. Available from: <https://doi.org/10.1002/hed.25072>.
- 55) Chitapanarux I, Traisathit P, Chitapanarux T, Jiratrach R, Chotaweesak P, Chakrabandhu S, et al. Arginine, glutamine, and fish oil supplementation in cancer patients treated with concurrent chemoradiotherapy: A randomized control study. *Current Problems in Cancer*. 2020;44(1):100482. Available from: <https://doi.org/10.1016/j.cuprprobncancer.2019.05.005>.
- 56) Dechaphunkul T, Arundon T, Raungkajon P, Jiratrach R, Geater SL, Dechaphunkul A. Benefits of immunonutrition in patients with head and neck cancer receiving chemoradiation: A phase II randomized, double-blind study. *Clinical Nutrition*. 2022;41(2):433–440. Available from: <https://doi.org/10.1016/j.clnu.2021.12.035>.
- 57) Barajas-Galindo DE, Vidal-Casariago A, Maza BPD, Fernández-Martínez P, Ramos-Martínez T, García-Arias S, et al. Postoperative enteral immunonutrition in head and neck cancer patients: Impact on clinical outcomes. *Endocrinol Diabetes Nutr (Engl Ed)*. 2019;67(1):13–19. Available from: <https://doi.org/10.1016/j.endinu.2019.05.006>.
- 58) Vidal-Casariago A, Calleja-Fernández A, Villar-Taibo R, Kyriakos G, Ballesteros-Pomar MD. Efficacy of arginine-enriched enteral formulas in the reduction of surgical complications in head and neck cancer: A systematic review and meta-analysis. *Clinical Nutrition*. 2014;33(6):951–957. Available from: <https://doi.org/10.1016/j.clnu.2014.04.020>.
- 59) Van Bokhorst-De Van Der Schueren MA, Quak JJ, Blomberg-Van Der Flier BMEV, Kuik DJ, Langendoen SI, Snow GB, et al. Effect of perioperative nutrition, with and without arginine supplementation, on nutritional status, immune function, postoperative morbidity, and survival in severely malnourished head and neck cancer patients. *The American Journal of Clinical Nutrition*. 2001;73(2):323–332. Available from: <https://doi.org/10.1093/ajcn/73.2.323>.
- 60) Armentano, Campos T, Barros CMdMR. Evidence on the use of arginine in response to inflammatory markers in patients with head and neck cancer: a Review. *Rev bras cir cabeça pescoço*. 2019. Available from: <https://www.epistemonikos.org/fr/documents/30eca87a7bc7e71ee808fa26bca9511b99a666dc#>.
- 61) Mochamat, Cuhls H, Marinova M, Kaasa S, Stieber C, Conrad R, et al. A systematic review on the role of vitamins, minerals, proteins, and other supplements for the treatment of cachexia in cancer: a European Palliative Care Research Centre cachexia project. *Journal of Cachexia, Sarcopenia and Muscle*. 2017;8(1):25–39. Available from: <https://doi.org/10.1002/jcsm.12127>.
- 62) Gröber U, Holzhauer P, Kisters K, Holick MF, Adamietz IA. Micronutrients in Oncological Intervention. *Nutrients*. 2016;8(3):163. Available from: <https://doi.org/10.3390/nu8030163>.
- 63) Pu Y, Zhu G, Xu Y, Zheng S, Tang B, Huang H, et al. Association Between Vitamin D Exposure and Head and Neck Cancer: A Systematic Review With Meta-Analysis. *Frontiers in Immunology*. 2021;12.
- 64) Yokosawa EB, Arthur AE, Rentschler KM, Wolf GT, Rozek LS, Mondul AM. Vitamin D intake and survival and recurrence in head and neck cancer patients. *The Laryngoscope*. 2018;128(11):371–376. Available from: <https://doi.org/10.1002/lary.27256>.
- 65) Izreig S, Hajek M, Edwards HA, Mehra S, Sasaki C, Bl J, et al. The role of vitamin D in head and neck cancer. *Laryngoscope Investig Otolaryngol*. 2020;5(6):1079–1088. Available from: <https://doi.org/10.1002/lto.2469>.
- 66) Bochen F, Balensiefer B, Körner S, Bittenbring JT, Neumann F, Koch A, et al. Vitamin D deficiency in head and neck cancer patients - prevalence, prognostic value and impact on immune function. *Oncoimmunology*. 2017;7(9). Available from: <https://doi.org/10.1080/2162402X.2018.1476817>.
- 67) Maturana-Ramírez A, Aitken-Saavedra J, Guevara-Benítez AL, Espinoza-Santander I. Hypovitaminosis D, oral potentially malignant disorders, and oral squamous cell carcinoma: a systematic review. *Medicina Oral Patología Oral y Cirugía Bucal*. 2022;27(2):e135–e141. Available from: <https://doi.org/10.4317/medoral.25049>.
- 68) Khamis A, Gül D, Wandrey M, Lu Q, Knauer SK, Reinhardt C, et al. The Vitamin D Receptor–BIM Axis Overcomes Cisplatin Resistance in Head and Neck Cancer. *Cancers*. 2020;14(20):5131. Available from: <https://doi.org/10.3390/cancers14205131>.
- 69) Afzal S, Bojesen SE, Nordestgaard BG. Low Plasma 25-Hydroxyvitamin D and Risk of Tobacco-Related Cancer. *Clinical Chemistry*. 2013;59(5):771–780. Available from: <https://doi.org/10.1373/clinchem.2012.201939>.
- 70) Fanidi A, Muller DC, Middttun Ø, Ueland PM, Vollset SE, Relton C, et al. Circulating vitamin D in relation to cancer incidence and survival of the head and neck and oesophagus in the EPIC cohort. *Scientific Reports*. 2016;6(1):1–11. Available from: <https://doi.org/10.1038/srep36017>.
- 71) Giovannucci E, Liu Y, Rimm EB, Hollis BW, Fuchs CS, Stampfer MJ, et al. Prospective Study of Predictors of Vitamin D Status and Cancer Incidence and Mortality in Men. *JNCI: Journal of the National Cancer Institute*. 2006;98(7):451–459. Available from: <https://doi.org/10.1093/jnci/djj101>.
- 72) Lipworth L, Rossi M, McLaughlin JK, Negri E, Talamini R, Levi F, et al. Dietary vitamin D and cancers of the oral cavity and esophagus. *Annals of Oncology*. 2009;20(9):1576–1581. Available from: <https://doi.org/10.1093/annonc/mdp036>.
- 73) Gugatschka M, Kiesler K, Obermayer-Pietsch B, Groselj-Strele A, Griesbacher A, Friedrich G. Vitamin D status is associated with disease-free survival and overall survival time in patients with squamous cell carcinoma of the upper aerodigestive tract. *European Archives of Oto-Rhino-Laryngology*. 2011;268(8):1201–1204. Available from: <https://doi.org/10.1007/s00405-010-1481-y>.
- 74) Gnagnarella P, Muzio V, Cainsi S, Raimondi S, Martinoli C, Chiocci S, et al. Vitamin D Supplementation and Cancer Mortality: Narrative Review of Observational Studies and Clinical Trials. *Nutrients*. 2021;13(9):3285. Available from: <https://doi.org/10.3390/nu13093285>.

- 75) Meyer F, Liu G, Douville P, Élodie Samson, Xu W, Adjei A, et al. Dietary vitamin D intake and serum 25-hydroxyvitamin D level in relation to disease outcomes in head and neck cancer patients. *International Journal of Cancer*. 2011;128(7):1741–1746. Available from: <https://doi.org/10.1002/ijc.25496>.
- 76) Akutsu T, Kitamura H, Himeiya S, Kitada S, Akasu T, Urashima M. Vitamin D and Cancer Survival: Does Vitamin D Supplementation Improve the Survival of Patients with Cancer? *Current Oncology Reports*. 2020;22(6):62. Available from: <https://doi.org/10.1007/s11912-020-00929-4>.
- 77) Nejatnamini S, Kubrak C, Álvarez Camacho M, Baracos VE, Ghosh S, Wismer WV, et al. Head and Neck Cancer Patients Do Not Meet Recommended Intakes of Micronutrients without Consuming Fortified Products. *Nutr Cancer*. 2018;70(3):474–482. Available from: <https://doi.org/10.1080/01635581.2018.1445767>.
- 78) De Munter L, Maasland DH, Van Den Brandt PA, Kremer B, Schouten LJ. Vitamin and carotenoid intake and risk of head-neck cancer subtypes in the Netherlands Cohort Study. *The American Journal of Clinical Nutrition*. 2015;102(2):420–432. Available from: <https://doi.org/10.3945/ajcn.114.106096>.
- 79) Nett H, Steegmann J, Tollkühn-Prött B, Hölzle F, Modabber A. A prospective randomized comparative trial evaluating postoperative nutritional intervention in patients with oral cancer. *Scientific Reports*. 2022;12(1). Available from: <https://doi.org/10.1038/s41598-022-18292-8>.
- 80) Sakhi AK, Bohn SK, Smeland S, Thoresen M, Smedshaug GB, Taus J, et al. Kjell Magne Russnes, Tone Svilaas & Rune Blomhoff (2010) Postradiotherapy Plasma Lutein,  $\alpha$ -Carotene, and  $\beta$ -Carotene Are Positively Associated With Survival in Patients With Head and Neck Squamous Cell Carcinoma. *Nutrition and Cancer*. 2010;62(3):322–328. Available from: <https://doi.org/10.1080/01635580903441188>.
- 81) Melo ADS, Dantas JBDL, Medrado ARAP, Lima HR, Martins GB, Carrera M. Nutritional supplements in the management of oral mucositis in patients with head and neck cancer: Narrative literary review. *Clinical Nutrition ESPEN*. 2021;43:31–38. Available from: <https://doi.org/10.1016/j.clnesp.2021.03.030>.
- 82) Chaitanya NC. Role of Vitamin E and Vitamin A in Oral Mucositis Induced by Cancer Chemo/Radiotherapy- A Meta-analysis. *Journal of Clinical & Diagnostic Research*. 2017;11(5). Available from: <https://doi.org/10.7860/jcdr/2017/26845.9905>.
- 83) Rao S, Kalekhan F, Hegde SK, Rao P, Suresh S, Baliga MS. Serum zinc status and the development of mucositis and dermatitis in head-and-neck cancer patients undergoing curative radiotherapy: A pilot study. *Journal of Cancer Research and Therapeutics*. 2022;18(1):42–48. Available from: [https://doi.org/10.4103/jcrt.jcrt\\_344\\_20](https://doi.org/10.4103/jcrt.jcrt_344_20).
- 84) Hoppe C, Kutschan S, Dörfler J, Büntzel J, Büntzel J, Huebner J. Zinc as a complementary treatment for cancer patients: a systematic review. *Clinical and Experimental Medicine*. 2021;21(2):297–313. Available from: <https://doi.org/10.1007/s10238-020-00677-6>.
- 85) Nascimento RB, Leite EGDS, Dantas JBDL, Costa TF, Martins GB, Carrera M, et al. Zinc supplementation in the management of oral mucositis in head and neck cancer patients: narrative literature review. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. 2022;134(3):E234. Available from: <https://doi.org/10.1016/j.oooo.2022.01.750>.
- 86) Shuai T, Yi LJJ, Tian X, Chen WQQ, Chen HQ, Li NE. Prophylaxis with oral zinc sulfate against radiation-induced oropharyngeal mucositis in patients with head and neck cancer. *Medicine*. 2018;97(48):e13310. Available from: <https://doi.org/10.1097/md.00000000000013310>.
- 87) Sharief R, Anandhi P, Rahila C. The benefit of zinc sulfate in oropharyngeal mucositis during hyperfractionated accelerated concomitant boost radiotherapy with concurrent cisplatin for advanced-stage oropharyngeal and hypopharyngeal cancers. *Indian Journal of Palliative Care*. 2020;26(4):437–443. Available from: [https://doi.org/10.4103/ijpc.ijpc\\_20\\_20](https://doi.org/10.4103/ijpc.ijpc_20_20).
- 88) Khan M, Siddiqui SA, Akram M, Alam M. Can zinc supplementation widen the gap between control and complications in head and neck cancer patients treated with concurrent chemo-radiotherapy. *Journal of Medical Sciences*. 2019;39(6):267. Available from: [https://doi.org/10.4103/jmedsci.jmedsci\\_20\\_19](https://doi.org/10.4103/jmedsci.jmedsci_20_19).
- 89) Shuai T, Tian X, Shi B, Chen H, Liu XL, Yi LJ, et al. Prophylaxis With Oral Zinc Sulfate Against Radiation Induced Oral Mucositis in Patients With Head and Neck Cancers: A Systematic Review and Meta-Analysis of Four Randomized Controlled Trials. *Frontiers in Oncology*. 2019;9:165. Available from: <https://doi.org/10.3389/fonc.2019.00165>.
- 90) Tian X, Liu XL, Pi YP, Chen H, Chen WQ. Oral Zinc Sulfate for Prevention and Treatment of Chemotherapy-Induced Oral Mucositis: A Meta-Analysis of Five Randomized Controlled Trials. *Frontiers in Oncology*. 2018;8:484. Available from: <https://doi.org/10.3389/fonc.2018.00484>.
- 91) Meneses AG, Normando AGC, De Toledo IP, Reis PED, Guerra ENS. Effects of oral supplementation in the management of oral mucositis in cancer patients: A meta-analysis of randomized clinical trials. *Journal of Oral Pathology & Medicine*. 2020;49(2):117–125. Available from: <https://doi.org/10.1111/jop.12901>.
- 92) Torgersen Z, Balters M. Perioperative Nutrition. *Surgical Clinics of North America*. 2015;95(2):255–267. Available from: <https://doi.org/10.1016/j.suc.2014.10.003>.
- 93) Martínez-Ortega AJ, Piñar-Gutiérrez A, Serrano-Aguayo P, González-Navarro I, Remón-Ruiz PJ, Pereira-Cunill JL, et al. Perioperative Nutritional Support: A Review of Current Literature. *Nutrients*. 2022;14(8):1601. Available from: <https://doi.org/10.3390/nu14081601>.
- 94) Moore C, Pegues J, Narisetty V, Spankovich C, Jackson L, Jefferson GD. Enhanced Recovery After Surgery Nutrition Protocol for Major Head and Neck Cancer Surgery. *OTO Open*. 2021;5(2). Available from: <https://doi.org/10.1177/2473974x211021100>.
- 95) Ljungqvist O. ERAS–enhanced recovery after surgery: moving evidence-based perioperative care to practice. *JPEN J Parenter Enteral Nutr*. 2014;38(5):559–566. Available from: <https://doi.org/10.1177/0148607114523451>.
- 96) Coyle MJ, Main B, Hughes C, Craven R, Alexander R, Porter GR, et al. Enhanced recovery after surgery (ERAS) for head and neck oncology patients. *Clinical Otolaryngology*. 2016;41(2):118–126. Available from: <https://doi.org/10.1111/coa.12482>.
- 97) Bertazzoni G, Testa G, Tomasoni M, Mattavelli D, Bon D, Montalto F, et al. The Enhanced Recovery After Surgery (ERAS) protocol in head and neck cancer: a matched-pair analysis. *Acta Otorhinolaryngol Ital*. 2022;42(4):325–333. Available from: <https://doi.org/10.14639/0392-100x-n2072>.
- 98) Prasad A, Chorath K, Barrette LX, Go B, Deng J, Moreira A, et al. Implementation of an enhanced recovery after surgery protocol for head and neck cancer patients: Considerations and best practices. *World J Otorhinolaryngol Head Neck Surg*. 2022;8(2):91–95. Available from: <https://doi.org/10.1002/wjo.2.20>.
- 99) Martindale RG, McClave SA, Taylor B, Lawson CM. Perioperative nutrition: what is the current landscape? *JPEN J Parenter Enteral Nutr*. 2013;37(5S):5–20. Available from: <https://doi.org/10.1177/0148607113496821>.
- 100) Nesemeier R, Dunlap N, McClave SA, Tennant P. Evidence-Based Support for Nutrition Therapy in Head and Neck Cancer. *Current Surgery Reports*. 2017;5(8):18. Available from: <https://doi.org/10.1007/s40137-017-0179-0>.
- 101) Head and Neck Guideline Steering Committee. Evidence-based practice guidelines for the nutritional management of adult patients with head and neck cancer. Sydney: Clinical Oncological Society of Australia. 2022. Available from: <https://wiki.cancer.org.au/australiawiki/index.php?oldid=215353>.
- 102) Dort JC, Farwell DG, Findlay M. Optimal Perioperative Care in Major Head and Neck Cancer Surgery With Free Flap Reconstruction: A Consensus Review and Recommendations From the Enhanced Recovery After Surgery Society. *JAMA Otolaryngol Head Neck Surg*. 2017;143(3):292–303. Available from: <https://doi.org/10.1001/jamaoto.2016.2981>.



- 103) Rowan NR, Johnson JT, Fratangelo CE, Smith BK, Kemerer PA, Ferris RL. Utility of a perioperative nutritional intervention on postoperative outcomes in high-risk head & neck cancer patients. *Oral Oncology*. 2016;54:42–46. Available from: <https://doi.org/10.1016/j.oraloncology.2016.01.006>.
- 104) Pogatschnik C, Steiger E. Review of Preoperative Carbohydrate Loading. *Nutrition in Clinical Practice*. 2015;30(5):660–664. Available from: <https://doi.org/10.1177/0884533615594013>.
- 105) Mörbe UM, Jørgensen PB, Fenton TM, Burg NV, Riis LB, Spencer J, et al. Human gut-associated lymphoid tissues (GALT); diversity, structure, and function. *Mucosal Immunology*. 2021;14(4):793–802. Available from: <https://doi.org/10.1038/s41385-021-00389-4>.
- 106) Stahl MG, Belkind-Gerson J. 1 - Development of the Gastrointestinal Tract. *Pediatric Gastrointestinal and Liver Disease (Sixth Edition)*. 2021;p. 2–10.e2. Available from: <https://doi.org/10.1016/b978-0-323-67293-1.00001-3>.
- 107) Szeffel J, Kruszewski WJ, Buczek T. Enteral feeding and its impact on the gut immune system and intestinal mucosal barrier. *Gastroenterology Review*. 2015;2(2):71–77. Available from: <https://doi.org/10.5114/pg.2015.48997>.
- 108) McClave SA, Taylor BE, Martindale RG. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition. *JPEN J Parenter Enteral Nutr*. 2016;40(8):159–211. Available from: <https://doi.org/10.1177/0148607115621863>.
- 109) Delaney SW, Shi H, Shokrani A, Sinha UK. Management of Chyle Leak after Head and Neck Surgery: Review of Current Treatment Strategies. *International Journal of Otolaryngology*. 2017;2017:1–12. Available from: <https://doi.org/10.1155/2017/8362874>.
- 110) Kawasaki N, Suzuki Y, Nakayoshi T, Hanyu N, Nakao M, Takeda A, et al. Early postoperative enteral nutrition is useful for recovering gastrointestinal motility and maintaining the nutritional status. *Surgery Today*. 2009;39(3):225–230. Available from: <https://doi.org/10.1007/s00595-008-3861-0>.
- 111) Kerauola CJ, Riva F, Paleri V. The impact of early oral feeding following head and neck free flap reconstruction on complications and length of stay. *Oral Oncology*. 2021;113:105094. Available from: <https://doi.org/10.1016/j.oraloncology.2020.105094>.
- 112) Crumley RL, Smith JD. Postoperative chylous fistula prevention and management. *The Laryngoscope*. 1976;86(6):804–813. Available from: <https://doi.org/10.1288/00005537-197606000-00008>.
- 113) Ilczyszyn A, Ridha H, Durrani AJ. Management of chyle leak post neck dissection: A case report and literature review. *Journal of Plastic, Reconstructive & Aesthetic Surgery*. 2011;64(9):e223–e230. Available from: <https://doi.org/10.1016/j.bjps.2010.12.018>.
- 114) Jiang H, Deng XF, Duan CM, Chen C, Xiang JL, Lu YL, et al. Somatostatin receptors SSTR2 and SSTR5 are expressed in the human thoracic duct. *Lymphology*. 2011;44(1):21–28. Available from: <https://pubmed.ncbi.nlm.nih.gov/21667819/>.
- 115) 2nd BG, Janis JE, Attinger CE. The basic science of wound healing. *Plast Reconstr Surg*. 2006;117(7):12S–34S. Available from: <https://doi.org/10.1097/01.prs.0000225430.42531.c2>.
- 116) Berbée C, Marx JP, Voelker MT, Schotte D, Bercker S. Parenteral nutrition in palliative care: single-centre observational study. *BMJ Supportive & Palliative Care*. 2022. Available from: <https://doi.org/10.1136/bmjspcare-2022-003581>.
- 117) Murai M, Higashiguchi T, Ohara H, Katsura N, Futamura A, Nakayama N. Multicentric prospective study of effect of dietary intake on quality of life for patients with end-stage cancers. *Fujita Med J*. 2020;6(1):1–6. Available from: <https://doi.org/10.20407/fmj.2018-023>.
- 118) Sánchez-Sánchez E, Ruano-Álvarez MA, Díaz-Jiménez J, Díaz AJ, Ordonez FJ. Enteral Nutrition by Nasogastric Tube in Adult Patients under Palliative Care: A Systematic Review. *Nutrients*. 2021;13(5):1562. Available from: <https://doi.org/10.3390/nu13051562>.
- 119) Druml C, Ballmer PE, Druml W, Oehmichen F, Shenkin A, Singer P, et al. ESPEN guideline on ethical aspects of artificial nutrition and hydration. *Clinical Nutrition*. 2016;35(3):545–556. Available from: <https://doi.org/10.1016/j.clnu.2016.02.006>.
- 120) Tagliaferri S, Lauretani F, Pelá G, Meschi T, Maggio M. The risk of dysphagia is associated with malnutrition and poor functional outcomes in a large population of outpatient older individuals. *Clinical Nutrition*. 2019;38(6):2684–2689. Available from: <https://doi.org/10.1016/j.clnu.2018.11.022>.
- 121) Reber E, Gomes F, Dähn IA, Vasiloglou MF, Stanga Z. Management of Dehydration in Patients Suffering Swallowing Difficulties. *J Clin Med*. 2019;8(11):1923. Available from: <https://doi.org/10.3390/jcm8111923>.