

Evidence-Based Support for Nutrition Therapy in Head and Neck Cancer

Ryan Neeseimer¹ · Neal Dunlap² · Stephen A. McClave³ · Paul Tennant¹

Published online: 6 July 2017
© Springer Science+Business Media, LLC 2017

Abstract

Purpose of Review Patients diagnosed with head and neck (H&N) cancer often present in a malnourished state for varied reasons; nutritional optimization is therefore critical to the success of treatment for these complex patients. This article aims to review the current nutrition literature pertaining to H&N cancer patients and to present evidence-based strategies for nutritional support specific to this population.

Recent Findings Aggressive nutritional intervention is frequently required in the H&N cancer patient population. Rehabilitating nutrition during operative and nonoperative treatment improves compliance with treatment, quality of life, and clinical outcomes. When and whether to establishing alternative enteral access are points of controversy, although recent evidence suggests prophylactic enteral feeding tube placement should not be universally applied. Perioperative nutritional optimization including preoperative carbohydrate loading and provision of arginine-supplemented immunonutrition has been shown to benefit at-risk H&N cancer patients.

Summary With multidisciplinary collaboration, H&N cancer patients can receive individualized nutritional support to withstand difficult cancer treatment regimens and return to acceptable states of nutritional health.

Keywords Malnutrition · Cachexia · Enteral nutrition · Immunonutrition

Introduction

Head and neck cancer represents 3–5% of all cancers diagnosed in the United States [1]. These malignancies can involve a variety of sites and tissues of origin, but the great majority of these tumors arise from the mucosal squamous epithelium of the upper aerodigestive tract as head and neck squamous cell carcinoma (HNSCC). The risk factors for this cancer cohort include tobacco use and regular alcohol consumption; the effect of these two substances on development of HNSCC is known to be synergistic [2]. These tumors also present more frequently in areas where the practice of betel nut chewing is prevalent [3]. More recently, human papilloma virus (HPV) has been implicated in the development of HNSCC, particularly oropharyngeal cancers [4]. In the last decade, the rise in HPV-related HNSCC has outpaced the decrement in non-HPV-related tumors [5].

The treatment of H&N cancer has historically focused on modalities that attain locoregional tumor control. Ablative surgery or radiation therapy represent the therapeutic backbone of most treatment regimens; often these treatment modalities are used in combination to effect cure. Over the last 40 years, primary treatment with nonsurgical intervention of chemotherapy and radiation has been used successfully to eradicate many tumors. While these

This article is part of the Topical collection on *Nutrition, Metabolism, and Surgery*.

✉ Paul Tennant
paul.tennant@louisville.edu

¹ Department of Otolaryngology-Head and Neck Surgery, University of Louisville, 529 S Jackson St., 3rd Floor, Louisville, KY 40202, USA

² Department of Radiation Oncology, University of Louisville, Louisville, KY, USA

³ Department of Medicine, Division of Gastroenterology, Hepatology, and Nutrition, University of Louisville School of Medicine, University of Louisville, Louisville, KY, USA

interventions spare surgical morbidity in many cases, they also inflict damage upon the swallowing mechanism that can be permanent [6]. Surgical salvage for tumor persistence/recurrence, nonfunctional swallowing apparatus, or osteoradionecrosis and soft tissue necrosis has become common; post-radiation surgical ablation is performed in about 20% of cases [7, 8].

The H&N cancer patient population represents a uniquely challenging cohort with respect to nutritional support. Not only does the inherent biology of cancer presence frustrate attempts to remediate nutritional deficiencies, but this heterogeneous group of patients often experiences swallowing deficiencies caused by tumor location and poor oral intake secondary to painful swallowing. These tumors are often diagnosed at a late stage when patients are already malnourished, and the multimodality treatment that is required to eradicate these malignancies often disrupts the swallowing apparatus, leaving patients dependent on gastrostomy tube feeds for enteral nutrition. The lack of social support, poor socioeconomic status, extensive history of smoking, and heavy alcohol use that is common in this patient population represent additional barriers to good nutrition during and after treatment for H&N cancer. Finally, the surgeries required to treat tumors of the head and neck often occur in previously irradiated tissues and frequently violate the barrier between the upper aerodigestive tract and the soft tissues of the neck; wound healing complications exceed 50% in many analyses, and poor nutritional status further compromises the potential to efficiently heal these wounds [7, 9].

Defining Malnutrition in the Head and Neck Cancer Population

While the nutritional deficiencies of the H&N cancer patient population have long been presumed, defining and quantifying these deficiencies has proven to be more challenging. Attempts to standardize the definition of malnutrition have been fraught with disagreement. A recent study identified deficiency of energy, deficiency of protein, and decreased fat-free mass as requisite elements in the definition of malnutrition, but a panel of experts disagreed regarding the relative importance of each. This disagreement extended to how malnutrition is operationally defined in clinical application [10]. These differences notwithstanding, there is general acceptance that low body mass index (BMI), involuntary weight loss, and decreased recent nutritional intake represent attributes consistent with a clinical diagnosis of malnutrition. For the purposes of standardization, malnutrition in HNSCC has been defined as unintentional weight loss >5–10% over the past

6 months and BMI <20 kg/m² [11–14]. Between 30 and 50% of patients meet the criteria for being malnourished at the time of HNSCC diagnosis [15].

Cancer cachexia is defined by Evans et al. as weight loss greater than 5% over the prior 12 months in the presence of cancer, plus 3 of the following criteria: decreased muscle strength, fatigue, anorexia, low fat-free mass index, and abnormal biochemical markers [16]. This entity has known unfavorable effects on quality of life, performance status, and physical function in HNSCC cancer patients. According to a recent meta-analysis, cancer cachexia is present in 20.2% of HNSCC patients at diagnosis and 32.2% of patients before initiation of treatment [17]. Not only are these patients physically, psychologically, and socially fragile [18–20], but the degree of their debilitation leads to increased treatment toxicity, interruptions in treatment course, and ultimately increased mortality, irrespective of treatment regimen employed [15, 21].

Subjective global assessment of nutrition was first proposed by Detsky et al. in 1987 and has since undergone several modifications [22•]. This validated screening tool has been used to identify patients who are nutritionally debilitated and it has been successfully applied in the cancer patient population to triage patients for treatment of malnutrition [23]. More recent efforts to correlate nutritional risk with patient outcome led to the nutritional risk screening (NRS) 2002, whereby patients are stratified based upon their degree of undernutrition and the severity of the disease process (Table 1). This screening mechanism was applied retrospectively to 128 randomized controlled trials comparing nutritional support to spontaneous intake and was found to reliably discriminate between trials that reported a positive outcome for dedicated nutritional intervention versus those that reported no difference between treatment groups [24•].

The use of serum markers to stratify nutritional risk is more controversial. Pretreatment hypoalbuminemia has been correlated with decreased disease-specific survival in HNSCC patients [25]. In a recent analysis of patients with H&N cancer of all types who underwent surgical ablation, low preoperative serum albumin was associated with an increased rate of wound infection and poorer overall survival. This effect on overall survival was most pronounced in patients with HNSCC [26]. Total serum protein, hemoglobin, transferrin, prealbumin, retinol-binding protein, neutrophil-lymphocyte ratio, and other inflammatory markers have variously been employed as surrogate measures for nutritional status. Serum prealbumin was found to be significantly lower in malnourished patients than in well-nourished patients undergoing radiotherapy for HNSCC [27]. Despite the purported correlation of certain laboratory values with poor patient outcomes and the incessant desire to identify a biomarker or battery of

Table 1 Screening for using NRS-2002

Impaired nutritional status		Severity of disease (stress metabolism)	
Absent	Normal nutritional status	Absent	Normal nutritional requirements
Score 0		Score 0	
Mild	Weight loss >5% in 3 months	Mild	Hip fracture
Score 1	OR	Score 1	Chronic patients, in particular with acute complications: cirrhosis, COPD
	Food intake <50–75% normal requirement in preceding week		Chronic hemodialysis, diabetes, oncology
Moderate	Weight loss >5% in 2 months	Moderate	Major abdominal surgery
Score 2	OR	Score 2	Stroke
	BMI 18.5–20.5 + impaired general condition		Severe pneumonia, hematologic malignancy
	OR		
	Food intake 25–50% of normal requirement in preceding week.		
Severe	Weight loss >5% in 1 month (~15% in 3 months)	Severe	Head injury
Score 3	OR	Score 3	Bone marrow transplantation
	BMI < 18.5 + impaired general condition		Intensive care patients (APACHE II > 10)
	OR		
	Food intake 0–25% of normal requirement in preceding week		
Total score			

APACHE Acute Physiologic and Chronic Health Evaluation; BMI body mass index, COPD chronic obstructive pulmonary disease, NRS-2002 Nutritional Risk Score 2002

biomarkers which could readily establish the diagnosis of malnutrition, current evidence does not support routine use of laboratory data to make treatment decisions regarding nutritional intervention. Expert consensus suggests that use of these serum markers in nutrition screening protocols “fails to appreciate the role of the inflammatory response on acute phase proteins that are often used as primary indicators of nutrition status [28].”

When the principles of aforementioned nutritional screening methodology are applied to the H&N cancer patient population, it is unsurprising that nutritional status is closely correlated with prognosis. The incidence of malnutrition is high in these patients and the extent of malnutrition is often substantial; unfortunately, the degree of nutritional derangement is invariably worse in patients with advanced-stage head and neck malignancies. Consequently, in order to provide appropriate nutritional intervention for at-risk patients, nutritional screening should be performed at the time of diagnosis. Percentage weight loss has shown good sensitivity and specificity for diagnosing malnutrition in the HNSCC patient population [11] and better accounts for malignancy-related nutritional derangement than BMI; this combined with a patient generated subjective global assessment (PG-SGA), ideally performed by a trained dietitian in the context of multidisciplinary cancer care, constitute basic requirements for

measuring nutritional status in the H&N cancer patient. The NRS 2002 represents an important adjunctive screening instrument for patients who will undergo surgical ablation as part of their treatment for H&N cancer, as it remains the best predictor of postsurgical complications.

Determining Need for Nutritional Intervention

Determining the most appropriate way to provide nutritional support during and after treatment for HNSCC requires a sophisticated understanding of the degree of malnutrition and swallowing dysfunction at the time of presentation and an awareness of the impact on swallowing that will result from treatment. Swallowing dysfunction is common in patients who present with HNSCC, and failure to recognize this condition can lead to worsening malnutrition or aspiration pneumonia, further debilitating the patient and hindering optimal treatment of the malignancy. Decisions regarding alimentation of HNSCC patients should therefore be made in a multidisciplinary treatment setting where speech language pathologists and dietitians can recommend interventions to preempt further nutritional depletion. Not infrequently, the degree of swallowing dysfunction will actually compel a certain course of treatment for the malignancy. An example of this situation

is in the case of advanced laryngeal malignancies, where anticipated poor swallowing outcome after nonsurgical, “organ-preserving” chemoradiation often leads to a recommendation of primary surgical treatment via total laryngectomy instead [29].

The effect of nonsurgical treatment of HNSCC on nutrition is well known. Over half of all patients who undergo radiotherapy for HNSCC lose weight [30]. The reasons for this are varied and include radiation-induced xerostomia and taste alterations, mucositis, difficulty masticating and swallowing, uncontrolled nausea, or constipation. Patients who experience weight loss have a higher incidence and longer duration of treatment-related morbidity [31]. Their treatment outcome is also ultimately affected, as >5% weight loss during radiation treatment for HNSCC has been associated with decreased disease-specific survival in multivariate analysis [32].

For patients undergoing radiotherapy and chemoradiotherapy, dietary counseling is mandatory and focuses on maintaining appropriate nutritional intake and preventing progression to a catabolic state with its attendant loss of lean muscle mass. Compliance with a designated nutritional regimen during radiotherapy resulted in improved body composition parameters in a recent study [33]. Current guidelines from the European Society for Parenteral and Enteral Nutrition (ESPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN) recommend that ambulating patients with cancer receive 1.2 to 2 g/kg/day of protein and 30 to 35 kcal/kg/day of energy daily [34, 35]. While Giles et al. found that adherence to these guidelines did not prevent weight loss in HNSCC patients who underwent primary radiotherapy and continued to take an oral diet [36], these standards represent a minimum intake goal for which to strive. Patients who achieved this level of dietary intake maintained quality of life through treatment without the need for more intensive nutritional counseling [37].

Route of Enteral Access

Another controversy in the nourishment of HNSCC patients is the route of enteral nutrition. While this patient population benefits from the fact that the lower gastrointestinal tract remains functional and parenteral nutrition therefore rarely needs to be utilized, swallowing function is often compromised at presentation, and therapeutic intervention, whether surgical or nonsurgical, invariably further deteriorates the swallowing mechanism. Surgical resection alters the anatomy and sometimes innervation of muscles critical to swallowing. Radiotherapy treatment toxicities include painful mucositis, altered taste, xerostomia, odynophagia, thickened secretions, and anorexia

[12, 38, 39]. Chemotherapy can exacerbate mucositis and cause nausea and vomiting [12, 40, 41].

Enteral nutrition via feeding tube placement is often necessary to provide a means of nutritional support without reliance on oral intake. The decision to place a feeding tube in a HNSCC patient pits the need for adequate nutrition and frequently nutritional rehabilitation against the objective of maintaining swallowing function by encouraging continued use of the muscles of deglutition without the “safety valve” of alternative enteral access. Indeed, evidence exists that patients who undergo prophylactic feeding tube placement prior to chemoradiation treatment have a longer duration of reliance on the feeding tube than patients who are treated reactively [42, 43]. Patients with stage III/IV HNSCC undergoing definitive chemoradiation who received prophylactic gastrostomy tube insertion were also more likely to develop esophageal stricture than a similar cohort who did not receive this intervention [44]. On the other hand, prophylactic feeding tube placement in HNSCC patients has been noted to improve quality of life and decrease the frequency of severe weight loss and hospital admissions [15, 21, 45]. As severe weight loss and poor quality of life are associated with treatment interruptions [46] which compromise tumor control [47], a compelling argument can be made to recommend early alternative enteral access to at-risk patients in order to promote timely completion of treatment.

The route of alternative enteral access has been debated. A recent Cochrane Review found a paucity of evidence comparing nasogastric (NG) tube feeding to gastrostomy feeding and could not recommend the use of one enteral feeding device over another [48]. Corry et al. studied reactive nasogastric feeding to gastrostomy feeding in HNSCC patients undergoing radiation or chemoradiation therapy and found that patients who received a percutaneous endoscopic gastrostomy (PEG) had significant initial weight gain compared to the NG tube-fed patients; a difference in weight gain was not observed between the groups 6 months posttreatment. Associated cost was ten times greater in the PEG group than the NG group, and the PEG group relied on the alternative enteral nutrition for a significantly longer period of time than the NG group. No difference in rate of chest infection was noted between the groups [49]. NG tube feeding is generally indicated if the anticipated length of requirement is less than four weeks. This route of nutrition has been associated with complications such as laryngeal irritation, persistent gastroesophageal reflux [50], and patient discomfort; increased risk of NG tube displacement or blockage has been noted when compared to PEG tube-fed HNSCC patients [49, 51]. It is the authors' experience that NG tube feeding is most efficacious in the perioperative inpatient setting when temporary NPO status is required for healing or swallowing

recovery is anticipated to occur quickly. Negative patient attitudes regarding persistent NG tube placement upon discharge and unwillingness of health care providers to administer NG tube feeds on an outpatient basis represent consistent barriers to continued NG tube feeding when a patient leaves the hospital.

While alternative enteral access is frequently unavoidable for HNSCC patients, there are known risks associated with placement of a gastrostomy tube. In current practice, gastrostomy tubes are placed endoscopically (PEG), radiologically (RIG), or by means of an open surgical procedure. Complications of feeding tube placement, including site infection, leakage around the gastrostomy site, local pain, gastric erosion, bowel perforation, and intraperitoneal leakage, vary widely between studies, likely due to reporting bias and differences in the definition of complications [43, 50]. Open surgical gastrostomy tube placement is generally considered a more significant intervention and is often eschewed in favor of less invasive techniques. In a 2009 meta-analysis comparing PEG and RIG placement in 2379 HNSCC patients, Grant et al. found that major complication rates following PEG and RIG were 7.4% (95% CI 5.9–9.3%) and 8.9% (95% CI 7.0–11.2%), respectively. Mortality rates were 2.2% (95% CI 0.014–0.034) for PEG and 1.8% (95% CI 0.010–0.032) for RIG [52]. These rates of complication and mortality in the HNSCC population are higher than previously reported rates in a mixed population [53], indicating that patients with HNSCC are more likely to experience morbidity and mortality associated with gastrostomy placement. When considering the provision of nutritional support via alternative route for HNSCC patients, concern must therefore be ascribed to the risks associated with feeding tube placement.

Another rare but important consideration in gastrostomy tube placement is the risk of abdominal wall metastasis via seeding. A recent retrospective analysis of HNSCC patients at a single institution revealed that 5 of 777 (0.64%) patients who underwent PEG developed abdominal wall metastasis over a 27.55 month average follow-up period [54]. A case series and literature review by Huang et al. in 2013 identified 42 cases of PEG site metastasis. Among this unfortunate cohort, 94.9% had Stage III/IV HNSCC at the time of diagnosis and the oropharynx was the most common primary tumor site; no patients had evidence of distant metastatic disease at presentation. The method of gastrostomy tube insertion was documented in 29 cases, with 28 (96.6%) reporting use of the Gauderer-Ponsky (“pull”) technique and one radiologically assisted placement. Duration from gastrostomy placement to diagnosis of gastrostomy site metastasis was 8 months, and patients generally expired within 6 months of diagnosis of PEG site metastasis [55].

Many HNSCC patients present with malnutrition, swallowing derangements, or inadequate oral intake; these patients generally require therapeutic feeding tube placement. Among patients without significant nutritional deficiency or swallowing issues precluding adequate oral intake at presentation, however, a proportion will nutritionally deteriorate during treatment despite efforts to maintain nutrition via oral intake. In an effort to balance the serious risks of nutritional debilitation and swallowing dysfunction in the HNSCC patient population with the risks of gastrostomy tube placement, recent efforts have focused on appropriate selection of patients who would benefit from prophylactic gastrostomy placement. Routine prophylactic PEG tube placement has been advocated in some centers as a way of reducing the risk of treatment interruptions during radiation therapy. Unfortunately, the aforementioned increased reliance on the PEG tube for nutrition and higher rate of esophageal stricture in patients who receive a prophylactic PEG tube represent undeniable disadvantages of an indiscriminate feeding tube placement strategy. One analysis showed that 47% of HNSCC patients who presented without dysphagia but received a prophylactic PEG prior to radiation or chemoradiation therapy did not use their feeding tubes or used them for less than two weeks [56]. A recent prospective trial of HNSCC patients referred for prophylactic PEG conveyed a markedly different experience, as 47 PEG tubes were placed in a cohort who received definitive chemoradiation therapy, and only 2 feeding tubes went unused. Nineteen percent of these patients who were in remission from their malignancy one year after treatment continued to require nutritional support via PEG tube [57]. The variation in these reports demonstrates the importance of utilizing appropriate selection criteria when determining which patients will be referred for prophylactic PEG tube placement.

Recent emphasis has been placed on identifying patient-related factors and anticipating treatment toxicity to decide which HNSCC patients should undergo prophylactic PEG tube placement. One group compared patient outcome data to an established set of guidelines for swallowing and nutrition management and distinguished advanced T-stage (T3 and T4) and administration of chemotherapy as predictive of need for prophylactic gastrostomy [58]. Another analysis concurred that the addition of chemotherapy to the treatment regimen in HNSCC patients undergoing radiation therapy portended need for PEG tube feeding while determining that higher pretreatment performance status (Karnofsky Performance Status ≥ 80) and gabapentin use were factors negatively associated with PEG use [59]. Using radiation dosimetric data, Matuschek et al. showed that negative performance status, chemotherapy administration, and radiation dose to the oropharynx independently predicted need for artificial nutrition on multivariate

analysis [60]. In a HNSCC sample who received surgical ablation as part of their treatment, patients who underwent gastrostomy placement either preoperatively or postoperatively were more likely to have complications and prolonged hospitalization compared to patients who did not undergo gastrostomy placement; interestingly, those patients who received a preoperative gastrostomy tube had reduced length of stay (LOS), less weight loss, and fewer wound complications compared to the cohort who received a gastrostomy tube postoperatively [61].

Perioperative Nutrition in Head and Neck Surgery

Among HNSCC patients who receive surgical ablation as part of their treatment, perioperative morbidity related to poor healing is frequently encountered. Nutritional optimization therefore represents a necessary objective in promoting recovery from these difficult procedures. Much of the basis for perioperative nutrition in head and neck cancer surgery is extrapolated from studies performed in patients who have undergone major abdominal surgery. While some preoperative physiologic parameters and responses to surgical stress are similar between these populations, surgical procedures performed on the HNSCC population have markedly different implications for speech, swallowing, and the aerodigestive tract, vary in length and anesthetic considerations, and often involve pedicled or free tissue transfer reconstruction. The inferences drawn from other surgical specialties with respect to perioperative nutrition must therefore be interpreted with caution. What remains certain is that these procedures frequently occur in nutritionally debilitated patients with unfavorable wounds and provoke a high degree of metabolic stress.

Preoperative Carbohydrate Loading

The surgical stress associated with lengthy procedures, including many H&N cancer resections, has been correlated with insulin resistance [62, 63]. Hyperglycemia secondary to insulin resistance increases perioperative morbidity and prolongs LOS, while strict blood glucose control in critically ill patients reduces morbidity and mortality [64, 65]. Starvation or fasting, common in the preoperative setting, has been linked to marked insulin resistance in healthy subjects [66]. Additionally, patient discomfort escalates during this time of fasting due to fatigue, thirst, hunger, and anxiety [67]. Preoperative carbohydrate loading has reduced insulin resistance by as much as 50% in colorectal surgery patients on postoperative day one [68]. This method of optimizing patients for

surgical stress is also associated with a reduction in the loss of lean body mass [69], muscle strength [70], and decreased length of hospitalization [71, 72]. A systematic review on the role of preoperative carbohydrate loading performed by Bilku et al. did not identify any convincing evidence of reduction in postoperative infections using this protocol [73]. Although not specifically researched in the HNSCC population, the principle of preoperative carbohydrate loading has become accepted in H&N cancer surgery [74]; it is our practice to recommend that patients ingest of an 800 mL 12.5% carbohydrate drink on the night before surgery and 400 mL on the morning of the procedure, consistent with Enhanced Recovery After Surgery (ERAS) Group recommendations [75].

Immunonutrition

The concept of immunonutrition for improved recovery after major head and neck surgeries has also been adapted from abdominal surgery best practices. HNSCC patients are at risk of similar postoperative complications such as infection, fistula formation, and locoregional malignant recurrence. The immunosuppressive condition of HNSCC patients has been associated with increased rates of post-surgical complications [76]. Arginine has been identified as a conditionally essential amino acid when metabolic stress occurs. It is obtained primarily from dietary intake and protein breakdown. Not only does arginine serve as a substrate in protein synthesis, but it is also a precursor for nitric oxide (NO), a potent vasodilator, and bactericidal agent. Additionally, elevated arginine levels increase collagen synthesis and stimulate lymphocyte and growth hormone production in experimental models and have therefore been postulated to improve wound healing [77]. Because HNSCC patients are susceptible to postoperative infections and poor wound healing and are often fed via tube feeds during the initial postoperative period, there is great interest in arginine-supplemented tube feed formulas. While an initial study of preoperative arginine-supplemented nutrition in malnourished H&N cancer patients established no conclusive benefit in clinical outcomes [78], this study might not have been adequately powered. More recent work has clearly shown that preoperative arginine-rich immunonutrition decreases perioperative infection rates and hospital LOS in H&N cancer patients [79, 80].

Nutritional supplementation with omega-3 fatty acids has also been proposed to improve perioperative wound healing in the HNSCC population. Once again, much of the evidence for this intervention is drawn from other surgical specialties. Perioperative outcome studies in other oncology patient populations have shown that nutritional supplementation with omega-3 fatty acids decreases ICU and

overall hospital LOS, reduces mortality, and decreases inflammatory response. This strategy has also been found to protect lean body mass after esophageal surgery [81], a finding corroborated in the HNSCC patient population [82].

The role of immunonutrition following H&N cancer surgery is well established. A 2008 systematic review analyzed 10 randomized controlled trials of immunonutrition in this patient population and found a significant reduction in the hospital LOS [83•]. A more recent systematic review and meta-analysis of nutritional supplementation in H&N cancer patients again demonstrated a reduction in the overall LOS (6.8 days) for patients who received arginine-supplemented immunonutrition [84]. The reason for decreased hospital LOS was not completely elucidated, as there was infrequent reporting of postoperative complications such as pneumonia, diarrhea, or cardiovascular events in the included studies. While the evidence equivocates somewhat regarding the benefit of immunonutrition in preventing postoperative complications among all HNSCC patients undergoing ablative surgery [83•], those patients who are malnourished preoperatively have significantly fewer postoperative wound infections when isolated as a subgroup [85]. This corresponds to the experience of Rowan, et al., who recently conducted a prospective, non-randomized trial comparing high-risk H&N cancer surgery patients (AJCC stage III or greater disease, prior definitive radiotherapy, use of a microvascular free flap for reconstruction) who were supplemented with arginine-rich immunonutrition before and after surgery to those who received standard formulations. The immunonutrition treatment arm demonstrated a significant reduction in pharyngeal leak and fistula formation (25 vs. 48%) and hospital LOS (2.8 days). Postoperative pneumonia was also decreased in the treatment cohort, but this difference did not achieve statistical significance. There was no difference in other postoperative wound infections, microvascular free flap failure or dehiscence, or bleeding complications between the two groups [76]. Another randomized, double-blinded, controlled trial included 32 malnourished HNSCC patients undergoing ablative surgery and found that patients who received arginine-supplemented nutrition for 10 days postoperatively had a median survival of 34.8 versus 20.7 months in the control group. Locoregional recurrence-free survival was also improved in the treatment arm. These differences were significant even after controlling for confounding variables [86].

The underlying mechanism by which immunonutrition confers a beneficial effect is unclear. A recent study has shown an increase in phosphatidylcholine/arachidonic acid ratio for well-nourished patients who receive immunonutrition compared to controls. Non-significant reductions in inflammatory markers (CRP, TNF-alpha, IL-6, IL-10) [87]

and faster rebound toward baseline levels of CD3+, CD4+, and CRP in patients who received immunonutrition have also been noted [88]. The authors of these studies hypothesize that immunonutrition lessens the postoperative inflammatory response. Although positive outcomes of immunonutrition vary between studies, it is important to note that no study has ever demonstrated a negative clinical impact of immunonutrition in the HNSCC population.

Calculating Postoperative Nutritional Requirements

Patients who are diagnosed with HNSCC often present in a malnourished state, and nutritional rehabilitation is not possible prior to requisite ablative surgery. While the risk of perioperative complications is substantial and most H&N surgical oncologists therefore intuitively favor aggressive postoperative protein and calorie nutritional goals, evidence-based postoperative nutritional recommendations specifically for the HNSCC population are lacking. The American College of Gastroenterology (ACG) recommends assessing every patient for their nutritional risk prior to initiation of enteral feedings using the NRS 2002 [24••] or NUTRIC Scoring system [89••]. Patients with higher nutritional risk benefit from more aggressive nutritional therapy, resulting in fewer complications [89••].

Determining the caloric requirement of postoperative HNSCC patients may be accomplished using indirect calorimetry or standard calculations. The ACG guidelines recognize indirect calorimetry (IC) as the most accurate measurement of caloric need but acknowledge that this tool is often unavailable or inaccessible [89••]. Also, inaccurate IC results may be obtained in critically ill ICU patients, patients who have endotracheal or tracheostomy tubes in which the ventilated gas is not completely captured, or patients with oxygen requirements exceeding 60% FiO₂ [90]. When IC is not feasible, weight-based equations are used to calculate nutritional goals. Caution should be applied, as these equations have often misrepresented actual caloric requirements in the postoperative setting [91]. On the other hand, a prospective study in surgical ICU patients that compared IC to the Harris-Benedict Equation (HBE), a popular energy requirement calculation, adjusted with a factor of 1.5 for activity and stress, and to a weight-based calculation of 30 kcal/kg/day adjusted body weight showed no significant difference in calculated calorie requirements between IC and the HBE with activity coefficient or the weight-based calculation [90]. In the HNSCC population, some authors have recommended caloric intake of 40–45 kcal/kg/day for repletion of nutrition after surgery [1, 92].

Protein supplementation has also been emphasized in the postoperative setting for HNSCC patients. Protein has

been identified as the most important macronutrient to consider when calculating nutritional goals, as its proper administration improves outcomes including mortality [89••, 93]. Previously, 1.2–1.5 g protein/kg/day was recommended; however, recent evidence suggests that protein intake of 2.0 g/kg/day or higher should be achieved to improve nitrogen balance [94]. Some authors recommend determining protein requirements by calculating nitrogen balance using 24-hour urine collection, although this may not be possible or feasible in all patients [89••]. Recognizing the malnourished and sarcopenic state of some HNSCC patients, Ardilio recommends calculating postoperative protein intake requirement in the hypermetabolic range of 1.5–2.5 g/kg/day and supplementing oral or enteral feedings with protein as necessary [92].

Timing and Route of Postoperative Nutrition

Timing of postoperative enteral feeding in the HNSCC population is the subject of active investigation. While the lower digestive tract is intact after most H&N ablative procedures, these patients have frequently undergone prolonged general anesthesia and may be slow to mobilize, predisposing them to feeding intolerance. Early enteral nutrition (initiating of feeding within the first 24 h of hospitalization) has many nutritional and non-nutritional benefits, especially in the critically ill patient [89••, 95]. The ACG guidelines recommend initiating enteral feedings within 24–48 h in the nutritionally high-risk patient and advancing to goal feeding within 48–72 h if tolerated; however, if the patient is not tolerating advancement, the schedule can be prolonged over 5–7 days [89••]. In data extrapolated from a population of severe burn patients, residual volumes of tube feeds remained elevated longer, and there was an increased rate of ileus in patients who had tube feed rate aggressively advanced compared to patients whose tube feeds rates were increased more slowly; no differences in hospital LOS or mortality were observed [95]. There are rare situations where underfeeding may be appropriate in the postoperative patient, including conditions of acute lung injury/acute respiratory distress syndrome (ARDS), obesity with a BMI >30, or recent history of parenteral nutrition (PN) over the first week of nutrition therapy [89••]. While there is evidence suggesting benefit of trophic feeding in ICU populations [96], caution must be employed when applying these findings to the HNSCC population, as the population under investigation was not representative of the HNSCC postoperative population [97]. Observational studies have shown that in critically ill patients who have a BMI <20, increasing calories reduces mortality [37]. Therefore, while trophic or underfeeding may be easier to initiate and maintain, the nutritional

benefits of goal enteral intake in this high-risk population cannot be understated and should be pursued except in extenuating circumstances [98].

For HNSCC patients who can safely take an oral diet postoperatively, prompt initiation of a protein- and calorie-rich diet is advocated. Often, a nasogastric tube is placed at the time of ablative surgery in order to temporarily bypass the swallowing mechanism and allow for timely administration of medication and enteral nutrition; patients in whom preoperative swallowing function is poor or whose swallowing is anticipated to be compromised by the ablative surgery commonly receive gastrostomy tube placement preoperatively or intraoperatively. Despite theoretical risk of damage to an oral cavity or pharyngeal anastomotic site after pedicled or microvascular free tissue transfer reconstruction, some centers even routinely perform PEG placement in the ICU in the postoperative setting. Parenteral nutrition is rarely employed postoperatively in H&N cancer surgery. When prolonged feeding intolerance occurs or when enteral nutrition cannot be safely delivered to the digestive tract, as in the case of a nasogastric tube that has been inadvertently removed across a fresh pharyngeal anastomotic site, total parenteral nutrition may be considered. This method of nourishment has also been applied in cases of postoperative chyle fistula when interruption of intestinal lymphatic flow is desired to promote spontaneous resolution of the fistula [99].

Postoperative nutrition strategies in H&N cancer patient should be conceived under the auspices of a registered dietician (RD) who is familiar with this population. The RD routinely determines caloric, protein, and free water goals, feeding schedules, and can even assist in the initiation of parenteral nutrition in select patients. The risk of refeeding syndrome must be heeded, as fluid and electrolyte shifts associated with resumption of enteral or parenteral feeding in malnourished patients places them at increased risk of mortality (Table 2) [100]. The HNSCC population represents a high-risk population for refeeding syndrome due to poor preoperative nutritional intake, increased metabolic demand, dysphagia, and high rates of alcoholism [100, 101]. The National Institute for Health and Care Excellence (NICE) guidelines have been used to identify patients at risk of refeeding syndrome; risk factors include low BMI (BMI < 16), unintentional weight loss >15% body weight within the previous 3–6 months, very little or no nutrient intake for >10 days, and low levels of potassium, phosphate, or magnesium prior to any feeding [102]. Additional risk factors that have been identified are increased age, low prealbumin or albumin, NRS-2002 score ≥ 3 [100].

In affirmation of the importance of the gastrointestinal microbiome during healing after abdominal surgery [103], perioperative probiotic use has been investigated in

Table 2 Criteria for determining people at high risk of developing refeeding problems as reported by the NICE guidelines

Patient has one or more	Patient has two or more
BMI < 16 kg/m ²	BMI < 18.5 kg/m ²
Unintentional weight loss >15% within last 3–6 months	Unintentional weight loss >10% within last 3–6 months
Little or no nutritional intake for >10 days	Little or no nutritional intake for >5 days
Low levels of potassium, phosphate, or magnesium prior to feeding	History of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics

BMI body mass index, NICE National Institute for Health and Clinical Excellence

patients who undergo surgery of the lower gastrointestinal tract. As many ablative H&N cancer surgeries communicate the soft tissues of the neck with the upper aerodigestive tract, perhaps the probiotic experience in abdominal surgery can be extrapolated to the H&N cancer population. Evidence currently suggests that the observed beneficial effects of probiotics are attributable to their ability to maintain the gut mucosal barrier and alter the innate immune response [104]. Two prospective randomized, controlled trials in colorectal surgery patients have demonstrated favorable outcomes with regard to surgical site infections and anastomotic leak as well as perioperative complications such as pneumonia when probiotics were administered [103, 105]. A recent systematic review and meta-analysis have also suggested beneficial effects of probiotics in this population [106, 107], although the degree of benefit is uncertain, and lack of standardization with regard to perioperative antibiotic use and probiotic administration among studies precludes recommendation of a specific probiotic regimen.

While the etiologic basis is poorly understood, evidence suggests that oral microbial colonization of healthy individuals is different than those affected by oral diseases [108]. A prior study has also shown alteration of the oral flora to more pathogenic species after radiation therapy in H&N cancer patients [109]. Nutritionally debilitated patients who undergo ablative procedures for H&N cancer, especially in salvage situations after prior radiation therapy, are therefore at particular risk for fistula formation and surgical site infections. Perioperative antibiotics are routinely given in this population, but probiotic administration may represent a novel adjunctive approach in preventing virulent microorganisms from compromising wound healing. Further investigation must be performed before this intervention can be routinely advocated.

Conclusion

Head and neck cancer patients often present in a malnourished state. The heterogeneity of these tumors with respect to the primary site, functional implications on

swallowing, and optimal treatment regimen renders broad prescriptive nutritional intervention problematic. An individualized approach to nutritional care of these patients is therefore mandatory for satisfactory treatment outcomes. For patients who undergo primary radiation or chemoradiation therapy, the desire to maintain swallowing function during the course of treatment must be balanced with the need for adequate nutritional intake. If nutritional supplementation via feeding tube is anticipated, the feeding tube should be placed prior to initiation of radiation so that the treatment course is not interrupted as a consequence of poor nutrition. Risk factors have been identified that portend need for alternative enteral access, and these should be heeded when the patient first establishes care.

In patients who undergo ablative surgery for treatment of H&N cancer, optimizing patients nutritionally and predicting the need for alternative enteral access postoperatively represent appropriate ways to minimize perioperative morbidity. Patients who receive primary ablative surgery also frequently require timely adjuvant treatment; minimizing surgical complications therefore improves adherence to standard H&N cancer treatment algorithms. Enteral nutrition can be maintained in H&N cancer patients with few exceptions. Immunonutrition with arginine-rich tube feed formulas improves perioperative outcomes. The postoperative administration of nutrition should be accomplished under the direction of a registered dietitian, using patient-specific parameters to establish nutritional requirements. As much of the evidence for perioperative nutritional support in H&N cancer patients is retrospective, single-institutional, or appropriated from other patient populations, future investigation offers robust opportunities to further understanding of optimal nutritional care in this challenging patient cohort.

Compliance with Ethics Guidelines

Conflict of interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
 - Of major importance
1. O'Neill PJ, Shaha AR. Nutrition management of patients with malignancies of the head and neck. *Surg Clin N Am*. 2011;91(3):631–9.
 2. Scully C. Oral cancer aetiopathogenesis; past, present and future aspects. *Med Oral Patol Oral Y Cir Bucal*. 2011;16(3):e306–11.
 3. Carpenter JM, Syms MJ, Sniezek JC. Oral carcinoma associated with betel nut chewing in the Pacific: an impending crisis? *Pac Health Dialog*. 2005;12(1):158–62.
 4. • Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst*. 2000;92(9):709–20. *Human papilloma virus is shown to have etiologic correlation with development of HNSCC*.
 5. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*. 2011;29(32):4294–301.
 6. Hutchesson KA, Lewin JS, Barringer DA, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. *Cancer*. 2012;118(23):5793–9.
 7. Gokhale AS, Lavertu P. Surgical salvage after chemoradiation of head and neck cancer: complications and outcomes. *Curr Oncol Rep*. 2001;3:72.
 8. Richey LM, Shores CG, George J, et al. The effectiveness of salvage surgery after the failure of primary concomitant chemoradiation in head and neck cancer. *Otolaryngol Head Neck Surg*. 2007;136(1):98–103.
 9. Zafareo M. Surgical salvage of recurrent cancer of the head and neck. *Curr Oncol Rep*. 2014;16:386.
 10. Meijers JM, van Bokhorst-de van der Schueren MA, Schols JM, et al. Defining malnutrition: mission or mission impossible? *Nutrition*. 2010;26(4):432–40.
 11. Ravasco P, Monteiro-Grillo I, Vidal PM, et al. Nutritional deterioration in cancer: the role of disease and diet. *Clin Oncol*. 2003;15(8):443–50.
 12. Beaver ME, Matheny KE, Roberts DB, Myers JN. Predictors of weight loss during radiation therapy. *J Otolaryngol Head Neck Surg*. 2001;125:645–8.
 13. van den Berg MG, Rasmussen-Conrad EL, van Nispen L, et al. A prospective study on malnutrition and quality of life in patients with head and neck cancer. *Oral Oncol*. 2008;44(9):830–7.
 14. Capuano G, Grosso A, Gentile PC, et al. Influence of weight loss on outcomes in patients with head and neck cancer undergoing concomitant chemoradiotherapy. *Head Neck*. 2008;30(4):503–8.
 15. van Bokhorst-de van der Schuer MA, van Leeuwen PA, Kuik DJ, et al. The impact of nutritional status on the prognoses of patients with advanced head and neck cancer. *Cancer*. 1999;86(3):519–27.
 16. Evans WJ, Morley JE, Argilés J, et al. Cachexia: a new definition. *Clin Nutr*. 2008;27(6):793–9.
 17. Couch ME, Dittus K, Toth MJ, et al. Cancer cachexia update in head and neck cancer: definitions and diagnostic features. *Head Neck*. 2015;37(4):594–604.
 18. Grobbelaar EJ, Owen S, Torrance AD, et al. Nutritional challenges in head and neck cancer. *Clin Otolaryngol Allied Sci*. 2004;29(4):307–13.
 19. Hammerlid E, Wirblad B, Sandin C, et al. Malnutrition and food intake in relation to quality of life in head and neck cancer patients. *Head Neck*. 1998;20(6):540–8.
 20. Ravasco P, Monteiro-Grillo I, Vidal PM, et al. Cancer: disease and nutrition are key determinants of patients' quality of life. *Support Care Cancer*. 2004;12(4):246–52.
 21. McRackan TR, Watkins JM, Herrin AE, et al. Effect of body mass index on chemoradiation outcomes in head and neck cancer. *Laryngoscope*. 2008;118:1180–5.
 22. •• Detsky AS, McLaughlin JR, Baker JP, et al. What is subjective global assessment of nutritional status? *JPEN J Parenter Enter Nutr*. 1987;11(1):8–13. *Subject global assessment is a mechanism for rigorously measuring nutrition and stratifying nutritional risk*.
 23. Bauer J, Capra S, Ferguson M. Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. *Eur J Clin Nutr*. 2002;56(8):779–85.
 24. •• Kondrup J, Rasmussen HH, Hamberg O, et al. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr*. 2003;22(3):321–36. *The NRS 2002 is a validated scale which stratifies nutritional risk with surgical outcomes*.
 25. Moon H, Roh JL, Lee SW, et al. Prognostic value of nutritional and hematologic markers in head and neck squamous cell carcinoma treated by chemoradiotherapy. *Radiother Oncol*. 2016;118(2):330–4.
 26. Danan D, Shonka DC Jr, Selman Y, et al. Prognostic value of albumin in patients with head and neck cancer. *Laryngoscope*. 2016;126(7):1567–71.
 27. Unal D, Orhan O, Eroglu C, Kaplan B. Prealbumin is a more sensitive marker than albumin to assess the nutritional status in patients undergoing radiotherapy for head and neck cancer. *Contemp Oncol*. 2013;17:276–80.
 28. White JV, Guenter P, Jensen G, et al. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *JPEN J Parenter Enter Nutr*. 2012;36(3):275–83.
 29. Lavoia JP, Ludlowa D, Morgan M, et al. Predicting feeding tube and tracheotomy dependence in laryngeal cancer patients. *Acta Otolaryngol*. 2017;137(3):326–30.
 30. Lees J. Incidence of weight loss in head and neck cancer patients on commencing radiotherapy treatment at a regional oncology centre. *Eur J Cancer Care*. 1999;8(3):133–6 (Engl).
 31. Johnston CA, Keane TJ, Prudo SM. Weight loss in patients receiving radical radiation therapy for head and neck cancer: a prospective study. *JPEN J Parenter Enter Nutr*. 1982;6:399–402.
 32. Langius JA, Bakker S, Rietveld DH, et al. Critical weight loss is a major prognostic indicator for disease-specific survival in patients with head and neck cancer receiving radiotherapy. *Br J Cancer*. 2013;109:1093–9.
 33. Hopanci Bicakli D, Ozkaya Akagunduz O, Meseri Dalak R, et al. The effects of compliance with nutritional counselling on body composition parameters in head and neck cancer patients under radiotherapy. *J Nutr Metab*. 2017;2017:8631945.
 34. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr*. 2017;36:11e48.
 35. August DA, Huhmann MB. American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N clinical guidelines: nutrition support therapy during adult anti-cancer treatment and in hematopoietic cell transplantation. *JPEN J Parenter Enter Nutr*. 2009;33(5):472–500.
 36. Giles KH, Kubrak C, Baracos VE, et al. Recommended European Society of Parenteral and Enteral Nutrition protein and energy intakes and weight loss in patients with head and neck cancer. *Head Neck*. 2016;38:1248–57.
 37. Roussel LM, Micault E, Peyronnet D, et al. Intensive nutritional care for patients treated with radiotherapy in head and neck

- cancer: a randomized study and meta-analysis. *Eur Arch Otorhinolaryngol.* 2017;274:977–87.
38. Ames JA, Kamell LH, Gupta AK, et al. Outcomes after the use of gastrostomy tubes in patients whose head and neck cancer was managed with radiation therapy. *Head Neck.* 2011;33(5):638–44.
 39. Backstrom I, Funegard U, Andersson I, et al. Dietary intake in head and neck irradiated patients with permanent dry mouth symptoms. *Eur J Cancer B Oral Oncol.* 1995;31B(4):253–7.
 40. Beer KT, Krause KB, Zuercher T, Stanga Z. Early percutaneous endoscopic gastrostomy insertion maintains nutritional state in patients with aerodigestive tract cancer. *Nutr Cancer.* 2005;52(1):29–34.
 41. Marcy P, Magne N, Bensadoun R, et al. Systematic percutaneous fluoroscopic gastrostomy for concomitant radiochemotherapy of advanced head and neck cancer; optimization of therapy. *Support Care Cancer.* 2000;8:410–3.
 42. Kramer S, Newcomb M, Hessler J, et al. Prophylactic versus reactive PEG tube placement in head and neck cancer. *Otolaryngol Head Neck Surg.* 2014;150:407–12.
 43. Chaudu A, Smith ACH, Douglas M. Percutaneous endoscopic gastrostomy in patients undergoing resection for oral tumors: a retrospective review of complications and outcomes. *J Oral Maxillofac Surg.* 2003;61:1279–84.
 44. Chen A, Li B, Lau DH. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemoradiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2010;78(4):1026–32.
 45. Agarwal E, Ferguson M, Banks M, et al. Malnutrition and poor food intake are associated with prolonged hospital stay, frequent readmissions, and greater in-hospital mortality: results from the Nutrition Care Day Survey 2010. *Clin Nutr.* 2013;32:737–45.
 46. Assenat E, Thezenas S, Flori N, et al. Prophylactic percutaneous endoscopic gastrostomy in patients with advanced head and neck tumors treated by combined chemoradiotherapy. *J Pain Symptom Manag.* 2011;42(4):548–56.
 47. Ames JA, Kamell LH, Gupta AK, et al. Outcomes after the use of gastrostomy tubes in patients whose head and neck cancer was managed with radiation therapy. *Head Neck.* 2011;33:638–44.
 48. 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 Syst Rev.* 2013. doi:10.1002/14651858.CD007904.pub3.
 49. Corry J, Poon W, McPhee N, et al. Randomized study of percutaneous endoscopic gastrostomy versus nasogastric tubes for enteral feeding in head and neck cancer patients treated with (chemo) radiation. *J Med Imaging Radiat Oncol.* 2008;52:503–10.
 50. Baredes S, Behin D, Deitch E. Percutaneous endoscopic gastrostomy tube feeding in patients with head and neck cancer. *Ear Nose Throat J.* 2004;83(6):417–9.
 51. Lees J. Nasogastric and percutaneous endoscopic gastrostomy feeding in head and neck cancer patients receiving radiotherapy treatment at a regional oncology unit: a two year study. *Eur J Cancer Care.* 1997;6(1):45–9.
 52. Grant D, Bradley P, Pothier D. Complications following gastrostomy tube insertion in patients with head and neck cancer: a prospective multi-institution study, systematic review, and meta-analysis. *Clin Otolaryngol.* 2009;34(2):103–12.
 53. Wollman B, D'Agostino HB, Walus-Wigle JR, et al. Radiologic, endoscopic, and surgical gastrostomy: an institutional evaluation and meta-analysis of the literature. *Radiology.* 1995;197:699–704.
 54. Fung E, Strosberg DS, Jones EL, et al. Incidence of abdominal wall metastases following percutaneous endoscopic gastrostomy placement in patients with head and neck cancer. *Surg Endosc.* 2016. doi:10.1007/s00464-016-5394-8.
 55. Huang AT, Georgiolos A, Espino S, et al. Percutaneous endoscopic gastrostomy site metastasis from head and neck squamous cell carcinoma: case series and literature review. *J Otolaryngol Head Neck Surg.* 2013;28(42):20.
 56. Madhoun MF, Blankenship MM, Blankenship DM, et al. Prophylactic PEG placement in head and neck cancer: how many feeding tubes are unused (and unnecessary)? *World J Gastroenterol.* 2011;17(8):1004–8.
 57. Moleiro J, Faias S, Fidalgo C, et al. Usefulness of prophylactic percutaneous gastrostomy placement in patients with head and neck cancer treated with chemoradiotherapy. *Dysphagia.* 2016;31(1):84–9.
 58. Findlay M, Bauer J, Brown T, et al. Evidence-based practice guidelines for the nutritional management of adult patients with head and neck cancer. Sydney: Cancer Council Australia. http://wiki.cancer.org.au/australia/COSA:Head_and_neck_cancer_nutrition_guidelines. Accessed on 12 Sept 2015.
 59. Yang W, McNutt TR, Dudley SA, et al. Predictive factors for prophylactic percutaneous endoscopic gastrostomy (PEG) tube placement and use in head and neck patients following intensity-modulated radiation therapy (IMRT) treatment: concordance, discrepancies, and the role of gabapentin. *Dysphagia.* 2016;31(2):206–13.
 60. Matuschek C, Bölke E, Geigis C, et al. Influence of dosimetric and clinical criteria on the requirement of artificial nutrition during radiotherapy of head and neck cancer patients. *Radiother Oncol.* 2016;120(1):28–35.
 61. Mays AC, Worley M, Ackall F, et al. The association between gastrostomy tube placement, poor post-operative outcomes, and hospital re-admissions in head and neck cancer patients. *Surg Oncol.* 2015;24(3):248–57.
 62. Thorell A, Nygren J, Ljungqvist O. Insulin resistance: a marker of surgical stress. *Curr Opin Clin Nutr Metab Care.* 1999;2(1):69–78.
 63. Thorell A, Efendic S, Gutniak M, Haggmark T, Ljungqvist O. Development of postoperative insulin resistance is associated with the magnitude of operation. *Eur J Surg.* 1993;159(11–12):593–9.
 64. Van den Berghe G, Wouters PJ, Bouillon R, Weekers F, Verwaest C, Schetz M, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. *Crit Care Med.* 2003;31(2):359–66.
 65. Kripsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc.* 2004;79(8):992–1000.
 66. Newman WP, Brodows RG. Insulin action during acute starvation: evidence for selective insulin resistance in normal man. *Metab Clin Exp.* 1983;32(6):590–6.
 67. Helminen H, Viitanen H, Sajanti J. Effect of preoperative intravenous carbohydrate loading on preoperative discomfort in elective surgery patients. *Eur J Anaesthesiol.* 2009;26(2):123–7.
 68. Nygren J, Soop M, Thorell A, Efendic S, Nair KS, Ljungqvist O. Preoperative oral carbohydrate administration reduces postoperative insulin resistance. *Clin Nutr.* 1998;17(2):65–71 (**Edinburgh, Scotland**).
 69. Yuill KA, Richardson RA, Davidson HI, Garden OJ, Parks RW. The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively—a randomised clinical trial. *Clin Nutr.* 2005;24(1):32–7.
 70. Henriksen MG, Hessov I, Dela F, Hansen HV, Haraldsted V, Rodt SA. Effects of preoperative oral carbohydrates and peptides on postoperative endocrine response, mobilization, nutrition and muscle function in abdominal surgery. *Acta Anaesthesiol Scand.* 2003;47(2):191–9.

71. Ljungqvist O, Nygren J, Thorell A. Modulation of post-operative insulin resistance by pre-operative carbohydrate loading. *Proc Nutr Soc.* 2002;61(3):329–36.
72. Noblett SE, Watson DS, Huong H, Davison B, Hainsworth PJ, Horgan AF. Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial. *Colorectal Dis.* 2006;8(7):563–9.
73. Bilku DK, Dennison AR, Hall TC, et al. Role of preoperative carbohydrate loading: a systematic review. *Ann R Coll Surg Engl.* 2014;96(1):15–22.
74. • 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. *The ERAS recommendations for major head and neck cancer surgery involving free flap reconstruction encourage evidence-based perioperative nutritional support obtained from other surgical oncology specialties.*
75. Lassen K, Soop M, Nygren J, et al. Enhanced Recovery After Surgery (ERAS) Group. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. *Arch Surg.* 2009;144(10):961–9.
76. 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 Oncol.* 2016;54:42–6.
77. Pierre JF, Heneghan AF, Lawson CM, Wischmeyer PE, Kozar RA, Kudsk KA. Pharmacconutrition review: physiological mechanisms. *JPEN J Parenter Enter Nutr.* 2013;37(5 Suppl):51s–65s.
78. van Bokhorst-De Van Der Schueren MA, Quak JJ, von Blomberg-van der Flier BM, Kuik DJ, Langendoen SI, Snow GB, et al. Effect of perioperative nutrition, with and without arginine supplementation, on nutritional status, immune function, post-operative morbidity, and survival in severely malnourished head and neck cancer patients. *Am J Clin Nutr.* 2001;73(2):323–32.
79. Felekis D, Eleftheriadou A, Papadakos G, et al. Effect of perioperative immuno-enhanced enteral nutrition on inflammatory response, nutritional status, and outcomes in head and neck cancer patients undergoing major surgery. *Nutr Cancer.* 2010;62(8):1105–12.
80. Aeberhard C, Mayer C, Meyer S, et al. MON-LB274: outcome after preoperative immunonutrition in head and neck squamous cell carcinoma patients. *Clin Nutr.* 2016;35:S254.
81. Gee AC, Kiraly L, McCarthy MS, et al. Nutrition support and therapy in patients with head and neck squamous cell carcinomas. *Curr Gastroenterol Rep.* 2012;14(4):349–55.
82. Weed HG, Ferguson ML, Gaff RL, et al. Lean body mass gain in patients with head and neck squamous cell cancer treated perioperatively with a protein- and energy-dense nutritional supplement containing eicosapentaenoic acid. *Head Neck.* 2011;33(7):1027–33.
83. • Stableforth WD, Thomas S, Lewis SJ. A systematic review of the role of immunonutrition in patients undergoing surgery for head and neck cancer. *Int J Oral Maxillofac Surg.* 2009;38(2):103–10. *The use of perioperative immunonutrition reduces postoperative hospital length of hospital stay compared to standard feeding formulas for head and neck cancer patients.*
84. Vidal-Casariago A, Calleja-Fernandez 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. *Clin Nutr.* 2014;33(6):951–7 (Edinburgh, Scotland).
85. Riso S, Aluffi P, Brugnani M, Farinetti F, Pia F, D'Andrea F. Postoperative enteral immunonutrition in head and neck cancer patients. *Clin Nutr.* 2000;19(6):407–12 (Edinburgh, Scotland).
86. Buijs N, van Bokhorst-de van der Schueren MA, Langius JA, Leemans CR, Kuik DJ, Vermeulen MA, et al. Perioperative arginine-supplemented nutrition in malnourished patients with head and neck cancer improves long-term survival. *Am J Clin Nutr.* 2010;92(5):1151–6.
87. Turnock A, Calder PC, West AL, et al. Perioperative immunonutrition in well-nourished patients undergoing surgery for head and neck cancer: evaluation of inflammatory and immunologic outcomes. *Nutrients.* 2013;5(4):1186–99.
88. Sorensen D, McCarthy M, Baumgartner B, et al. Perioperative immunonutrition in head and neck cancer. *Laryngoscope.* 2009;119(7):1358–64.
89. •• McClave SA, DiBaise JK, Mullin GE, et al. ACG clinical guideline: nutrition therapy in the adult hospitalized patient. *Am J Gastroenterol.* 2016;111(3):315–34. *Updated guidelines for nutritional therapy in adult hospitalized patients are proposed, including the proper use of enteral access, formula selection, and parenteral nutrition use.*
90. Davis KA, Kinn T, Esposito TJ, et al. Nutritional gain versus financial gain: the role of metabolic carts in the surgical ICU. *J Trauma Acute Care Surg.* 2006;61(6):1436–40.
91. Tignanelli CJ, Andrews AG, Sieloff KM, Pleva MR, Reichert HA, Wooley JA, et al. Are predictive energy expenditure equations in ventilated surgery patients accurate? *J Intensive Care Med.* 2017. doi:10.1177/0885066617702077.
92. Ardilio S. Calculating nutrition needs for a patient with head and neck cancer. *Clin J Oncol Nurs.* 2011;15(5):457–9.
93. Allingstrup MJ, Esmailzadeh N, Wilkens Knudsen A, Espersen K, Hartvig Jensen T, Wiis J, et al. Provision of protein and energy in relation to measured requirements in intensive care patients. *Clin Nutr.* 2012;31(4):462–8 (Edinburgh, Scotland).
94. Dickerson RN, Pitts SL, Maish GO 3rd, Schroepel TJ, Magnozzi LJ, Croce MA, et al. A reappraisal of nitrogen requirements for patients with critical illness and trauma. *J Trauma Acute Care Surg.* 2012;73(3):549–57.
95. Kesey J, Dissanaika S. A protocol of early aggressive acceleration of tube feeding increases ileus without perceptible benefit in severely burned patients. *J Burn Care Res.* 2013;34(5):515–20.
96. Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA.* 2012;307(8):795–803.
97. McClave SA, Codner P, Patel J, Hurt RT, Allen K, Martindale RG. Should we aim for full enteral feeding in the first week of critical illness? *Nutr Clin Pract.* 2016;31(4):425–31.
98. Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. *Intensive Care Med.* 2009;35(10):1728–37.
99. Bozzetti F, Arullani A, Baticci F, et al. Management of lymphatic fistulas by total parenteral nutrition. *JPEN J Parenter Enter Nutr.* 1982;6(6):526–7.
100. Friedli N, Stanga Z, Sobotka L, Culkin A, Kondrup J, Laviano A, et al. Revisiting the refeeding syndrome: results of a systematic review. *Nutrition.* 2017;35:151–60.
101. Ahmed S, Travis J, Mehanna H. Re-feeding syndrome in head and neck-prevention and management. *Oral Oncol.* 2011;47(9):792–6.
102. National Collaborating Centre for Acute C. National Institute for Health and Clinical Excellence: Guidance. Nutrition Support for Adults: Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition. London: National Collaborating Centre for Acute Care (UK).
103. Kotzampassi K, Stavrou G, Damoraki G, et al. A four-probiotics regimen reduces postoperative complications after colorectal

- surgery: a randomized, double-blind, placebo-controlled study. *World J Surg.* 2015;39(11):2776–83.
104. Stavrou G, Giamarellos-Bourboulis EJ, Kotzampassi K. The role of probiotics in the prevention of severe infections following abdominal surgery. *Int J Antimicrob Agents.* 2015;46(Suppl 1):S2–4.
105. Sadahiro S, Suzuki T, Tanaka A, et al. Comparison between oral antibiotics and probiotics as bowel preparation for elective colon cancer surgery to prevent infection: prospective randomized trial. *Surgery.* 2014;155(3):493–503.
106. He D, Wang HY, Feng JY, et al. Use of pro-/synbiotics as prophylaxis in patients undergoing colorectal resection for cancer: a meta-analysis of randomized controlled trials. *Clin Res Hepatol Gastroenterol.* 2013;37(4):406–15.
107. Lytvyn L, Quach K, Banfield L, et al. Probiotics and synbiotics for the prevention of postoperative infections following abdominal surgery: a systematic review and meta-analysis of randomized controlled trials. *J Hosp Infect.* 2016;92(2):130–9.
108. Bizzini B, Pizzo G, Scapagnini G, et al. Probiotics and oral health. *Curr Pharm Des.* 2012;18(34):5522–31.
109. Schuurhuis JM, Stokman MA, Witjes MJ, et al. Head and neck intensity modulated radiation therapy leads to an increase of opportunistic oral pathogens. *Oral Oncol.* 2016;58:32–40.