Review Article

Preoperative nutritional optimization of esophageal cancer patients

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Abstract: Optimization of the nutritional and metabolic state prior to major surgery leads to improved surgical outcomes and is increasingly seen as an important part of oncology disease management. For locally advanced esophageal cancer the treatment is multimodal, including neoadjuvant chemoradiotherapy or perioperative chemotherapy in combination with esophageal resection. Patients undergoing such a multimodal treatment have a higher risk for progressive decline in their nutritional status. Preoperative malnutrition and loss of skeletal muscle mass has been reported to correlate with unfavorable outcomes in patients who undergo esophageal cancer surgery. Decline in nutritional status is most likely caused by insufficient nutritional intake, reduced physical activity, systemic inflammation and the effects of anticancer therapy. To ensure an optimal nutritional status prior to surgery, it is key to assess the nutritional status in all preoperative esophageal cancer patients, preferable early in the treatment trajectory, and to apply nutritional interventions accordingly. Nutritional management of esophageal cancer can be challenging, the optimal nutritional therapy is still under debate, and warrants more nutritional scientific research. In this review, the most recent findings regarding preoperative nutrition associated with outcomes in patients with esophageal cancer will be explored.

Keywords: Esophageal neoplasms; malnutrition; cachexia; nutritional status; preoperative care

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Introduction

A major challenge for those living with esophageal cancer is the impact of the disease and treatment on nutritional status and ultimately, quality of life (QoL). These patients are often malnourished at diagnosis due to local tumor effects causing symptoms such as dysphagia, vomiting, inadequate nutritional intake, fatigue, weight and muscle loss (1-3), resulting in a suboptimal state for treatment (4-7). Malnutrition is related to adverse outcomes in active cancer treatments, including toxicity to chemotherapy agents and poor surgical outcomes, and is an independent factor in predicting survival (4,6-10).

For localized esophageal cancer, neoadjuvant chemoradiotherapy or perioperative chemotherapy followed by esophagectomy is increasingly applied worldwide as the curative treatment trajectory (11), with a 5-year disease survival rate around 50% (12).

Esophagectomy is a complex surgical procedure that is associated with relatively high surgery-related complications, morbidity and mortality (13), and a poor long-term QoL (14). Strategies to improve outcome could be preoperative individual risk assessment, pre-optimization strategies, use of multimodality treatment, centralization of esophageal cancer surgery, use of minimally invasive esophagectomy techniques and an enhanced recovery pathway (1,15).

The integration of appropriate nutritional care into the overall management of patients with esophageal cancer is of utmost value: from diagnosis, through the treatment trajectory and during remission (1,16). The interval time between neoadjuvant therapy and surgery offers the possibility to correct deterioration in the nutritional status before the esophagectomy is performed.

This review provides an overview of the current literature about preoperative nutritional management strategies to prepare patients for surgery (see *Table 1*).

Table 1 Overview nutritional strategies for optimization of esophageal cancer patients before surgery

Screen and assess the nutritional status regularly, at diagnosis, during neoadjuvant therapy and prior to surgery
Make diagnostic assessment on all domains of malnutrition: weight change, BMI, body composition (skeletal muscle mass), dietary intake, physical activity and performance and degree of inflammation
Start early nutritional support, before pronounced metabolic abnormalities
If possible measure resting energy expenditure, especially in patients with abnormal body composition and/or weight BMI range and/or high levels of inflammation
If possible measure body composition and use fat free mass/skeletal muscle mass for calculating protein requirements
Encourage patients to combine protein-rich food/supplements with physical exercise due to their synergetic effect
Encourage patients not drinking alcohol 4 weeks prior to surgery
Avoid prolonged fasting prior to esophagectomy: 6 hours for solid foods, 2 hours for clear liquids, carbohydrate drinks up to 2 hours preoperative
No clear evidence for immunonutrition
Preoperative personalized counseling on nutritional targets and goals stimulates the patients' own role in recovery and facilitate adherence to the care pathway

Malnutrition

Patients with esophageal cancer usually experience significant weight loss and have a high risk for malnutrition (2,17), because both the severity of the illness and the multimodal oncological treatment threatens patients' nutritional status. Malnutrition results from an inadequate intake or absorption of nutrients and leads to measurable adverse effects on body weight, body composition, function and clinical outcomes (18). In cancer patients, malnutrition is triggered by a disease-specific inflammatory response, also called cancer cachexia (2,18,19). Cancer cachexia is a multifactorial process of skeletal muscle loss, with or without loss of adipose tissue, resulting in involuntary weight loss and physical function decline. It is a process which cannot reverse completely by nutrition support alone (19). The pathophysiology of cachexia is complex and still not entirely clarified, but there seems to be a negative protein and energy balance probably due to a combination of reduced nutrient intake and altered metabolism (19). At the time of diagnosis, 80% of the patients have over 16% involuntary weight loss (20). This weight loss can be caused by reduced food intake in the presence of dysphagia, which is a common presenting symptom at diagnosis (1). Systemic inflammation induced by tumor factors, in turn leads to increased energy expenditure and an altered macronutrient metabolism which enhances weight loss, and specific skeletal muscle loss (2,21). The side effects of the neoadjuvant chemoradiotherapy or chemotherapy (e.g., nausea, vomiting, diarrhea, dysphagia caused by esophagitis) can be an additional reason for deterioration in nutritional status and possible even leading to severe malnutrition before surgery (22).

To date, limited research has been done to address the influence of esophageal cancer cachexia on postoperative outcomes. A cohort study (N=922) has showed that severe involuntary weight loss (≥10%) before esophageal cancer surgery is associated with worse overall five-year survival but does not seem to effect the risk of surgical complications or hospital length of stay, compared with no or limited weight loss (23). Another cohort study (N=390) found that a preoperative weight loss of >10% might also increase mortality after esophagectomy (24). A retrospective study (N=388) reported that underweight (BMI <18.5) esophageal cancer patients are at increased risk for postoperative pulmonary and other complications (25). Malnutrition could cause respiratory muscle weakness, leading to an increased incidence of postoperative respiratory complications, such as pulmonary infection (26). Dietitian-delivered intensive nutritional support for all patients with esophageal cancer is significantly associated with greater neoadjuvant therapy completion rates, less serious complications after esophagectomy, fewer hospital stays and overall less weight loss (27).

In general and gastrointestinal surgery, preoperative malnutrition is associated with worse outcomes (4,6-8,28).

In the recent years, there has been an increasing amount of studies on the assessment of body composition for the diagnostic purpose of cancer cachexia and sarcopenia as prognostic factors in patients with esophageal cancer. Sarcopenia, i.e., muscle failure, is defined as a muscle disease rooted in adverse muscle changes which accrue across a lifetime and is defined by low levels of muscle strength, muscle quantity and quality and physical performance as an indicator of severity (29), and can occur concurrently with obesity (30). Estimates of sarcopenia prevalence in esophageal cancer patients prior to surgery vary from 16% to 75%, depending on definition and assessment methods used and esophageal cancer type and staging (31).

A recent systematic review and meta-analysis, including 29 studies in 3,193 patients with esophageal cancer, summarized the existing evidence regarding the current methods to assess body composition and sarcopenia and to explore its use in clinical practice for predicting outcomes (31). The body composition measurement methods used in the included studies are computed tomography (N=18 studies), bioelectric impedance analysis (N=10 studies) and one study dual-energy X-ray absorptiometry. Significant differences were found in study design, used sarcopenia definitions and cut-off points and/or techniques used for muscle measurement. However, this systematic review and meta-analysis showed that preoperative sarcopenia leads to a higher incidence of pulmonary complications and is associated with a reduced overall survival, but is not associated with early mortality and overall postoperative complications after esophagectomy (31).

Sarcopenia is a hallmark sign of frailty. Frailty is defined as a clinically recognizable state of increased vulnerability due to physiologic stressors resulting from aging and has been associated with a decreased physiologic reserve and decrease in function across multiple physiological systems (32). Frailty is a strong predictor for short- and long-term outcome following complicated (upper) gastrointestinal surgery (32,33).

One retrospective study in patients with esophageal cancer used a frailty score for preoperative risk assessment. They found that the morbidity and mortality rates significant increased as the frailty index increases (34).

It seems important to screen for malnutrition in all patients with cancer-cachexia, sarcopenia and frailty, to identify overlap with these syndromes and to recognize the need for nutritional interventions within this group (35). In addition, it is recommended to combine nutritional interventions with exercise training, for maintaining or improving the nutritional status and physical reserve (4).

Screening and assessment of malnutrition

As preoperative malnutrition is associated with an adverse surgical outcome, the integration of early screening for malnutrition and appropriate nutritional support into the overall preoperative management of patients with esophageal cancer is important (4,15,17,36). The risk for late detection of malnutrition exists as patients often do not manifest symptoms early in the disease trajectory. An intervention is more likely to be effective when initiated early, before pronounced metabolic abnormalities produce resistance to nutritional intervention (4,37).

Nutrition-risk screening aims to increase awareness allowing early recognition and treatment (4). Several brief, practical and validated screening tools are available and can be used for patient with cancer (4,38,39). Recently, the European Society for Clinical Nutrition and Metabolism (ESPEN) recommended preoperative nutrition support in patients who at least met one of the following criteria: severe weight loss (>10–15% in 6 months), low body mass index (BMI <18.5 kg/m^2), Subjective Global Assessment Grade C, or serum albumin <30 g/L (in the absence of hepatic or renal failure) (7). These criteria define a high risk of malnutrition as well as disease associated catabolism. Hypoalbuminemia is a well-documented surgical risk factor (7). Hypoalbuminemia is, however, more a reflection of the extent of physiologic stress resulting from disease of treatment-related inflammation rather than the lack of adequate nutritional intake or malnutrition (40-42).

A high nutritional risk screening must be followed by an extensive diagnostic nutritional assessment to establish the nutritional status and to design the optimal nutritional therapy for the patient (4). Even in patients without weight loss or malnutrition, timely nutritional support might be beneficial to maintain the nutritional status if patients experience eating problems preoperative.

There is no consensus on criteria for the diagnosis of malnutrition in cancer patients, but it is recommended to assess dietary intake, weight history, body composition (muscle mass), physical activity and performance and the degree of systemic inflammation (2,4,43). Ideally this assessment is done by a qualified dietitian to determine the need for nutritional intervention and should be undertaken in all patients before surgery (1,4,15).

Weight loss and low BMI are often used as parameters for (the risk of) malnutrition in cancer patients (5), but these parameters do not provide reliable information on body composition, in particular muscle mass and quality (5,19).

Due to this, assessment of body composition is becoming clinically important in recent years, in addition to weight loss and BMI assessment.

The Patient-Generated Subjective Global Assessment (PG-SGA) is recommended as nutritional assessment tool in various countries and/or included in various guidelines for nutrition in oncology (39) and is recently included in a guideline for esophageal cancer patients in Taiwan (17). The PG-SGA (full and Short Form) covers all domains of the conceptual definitions of malnutrition, as defined by ESPEN and the American Society of Enteral and Parenteral Nutrition (ASPEN) (44). In a recent Asian cross-sectional study the PG-SGA was found to be strongly correlated with the Karnofsky and Eastern Cooperative Oncology group (ECOG) performance status (45).

In order to reach international consensus, the Global Leadership Initiative on Malnutrition (GLIM) published in 2018 three phenotypic and two etiologic criteria for the diagnosis and grading of malnutrition in clinical settings (35). Validation studies on the new criteria will follow in the next few years.

Preoperative nutrition therapy

The main goals of nutrition therapy are to prevent or treat early malnutrition and catabolism from the time of diagnosis to reduce treatment-related morbidity and improve QoL (2).

Nutrition goals include provision of an adequate nutritional intake to prevent loss of muscle mass, modulate inflammation and the immune response, optimize glucose control, attenuate the hypermetabolic response to surgery, and to provide micro- and macronutrients to optimize healing and recovery (46,47). Nutrition supplementation can promote a shift to the anabolic state (46-48).

Preoperative nutrition therapy has to be implemented for 7–10 days to optimize the mildly malnourished patient (7). In patients with a high risk for malnutrition a minimum of 10–14 days of nutritional therapy combined with resistance exercise preceding major surgery is highly recommended (7). Patients with low physical reserves, especially the sarcopenic and frail patients, could benefit more from 4–5 weeks of multimodal therapy with a nutrition and physical exercise component due to their strong synergistic effect on muscle protein synthesis (7,9). An ongoing multicenter RCT trial is currently examining the effect of a multimodal prehabilitation program during neoadjuvant chemotherapy on complete oncology treatment outcome in patients with esophageal and gastric cancers (49).

More research is needed on the optimal duration of preoperative nutritional support for malnourished patients (28,47).

Literature on the optimal energy, macro- and micronutrients requirements for surgical and cancer patients is limited (4,7), and not yet available for patients with esophageal cancer. Recent nonsurgical oncology guidelines recommend a target range of 25–30 kcal/kg/day with 1–1.5 g protein/kg/day and daily use of a multivitamin-multimineral supplement consisting of the recommended daily allowance (RDA) (4).

Using standard formulas for the calculation of energy requirements, such as 25–30 kcal/kg/day, under- (40%) or overestimate (30%) the individual energy demand in patients with cancer, which can lead to inaccurate dietary treatment of the patients (2,50). Increased as well as decreased energy expenditure (hypo- and hypermetabolism) in patients with cancer is reported (50). One in four patients with gastrointestinal cancer shows a hypermetabolic state (51). One study in patients with esophageal cancer reported significant elevated resting energy expenditure (REE) levels at diagnosis (52). REE is an important determinant of total daily energy expenditure. Individual energy requirements are most accurately determined by indirect calorimetry and are recommended to use in cancer patients, especially in those with high levels of inflammation, abnormal body composition and/or weight BMI range (4). Indirect calorimetry measures energy expenditure through evaluating the use of energy substrates based on the consumption of oxygen and the concomitant production of carbon dioxide. It has been considered the most accurate method for determining REE. However, in routine clinical practice, calorimeters are not regularly available, and energy requirements are estimated based on prediction formulas (2).

Future research should explore the actual energy demands in patients with esophageal cancer during their treatment trajectory, to optimize energy requirement for improving the nutritional status in this patient group.

Though it has been well established that a high protein intake is important to promote muscle protein anabolism in patients with cancer (4,43,53), less information is available on the optimal amount of protein intake. Recommendations vary between 1.0 g protein/kg/day to a target of 1.2–2.0 g protein/kg/day (4,7,54). Similar to estimating the energy requirements, the current protein equations rely on a patients' total body weight and fail to account for various changes in body composition in patients with cancer (53).

Good quality protein from poultry, fish, dairy, eggs, and plant represent sources supply the primary source of protein (9), and supplementation should be prescribed only if necessary (4). There are promising results with whey protein or essential amino acid supplementation (28,53) and using a bolus of 20–35 g of protein per meal (9,28) to stimulate muscle protein synthesis. New studies should focus on the optimal source, amount and timing of protein intake, with or without exercise therapy, for maximal stimulation of muscle protein synthesis in patients with esophageal cancer.

The optimal nutritional approach for patients with resectable esophageal cancer undergoing neoadjuvant treatment before esophagectomy has yet to be determined (55). Intensive nutritional counseling and a personal high energy, high protein oral diet is the first choice nutrition treatment (1,2,4,56). Patient engagement is facilitated by educating them on the role they can play in accelerating their own recovery (56). Dietary advice to deal with or to decrease the gastrointestinal symptoms (e.g., dysphagia, mucositis, anorexia) and dividing daily intake to smaller and more frequent meals as well as modifications of food consistency may be necessary (1,2). The additional use of oral protein and energy supplements are recommended when the oral intake is inadequate or when malnutrition is already present (4,7,15,28).

Enteral, and if enteral delivery is not sufficient parenteral, nutrition is recommended if patients have inadequate oral intake (4,6,7,28), described as no oral nutrient intake for more than a week or an energy oral intake of <60% of requirement for more than 1–2 weeks (4).

Immunonutrition

Immune modulating nutrients (e.g., arginine, omega-3 fatty acids, and nucleotides) are hypothesized to have a positive modulatory effect on immune and inflammatory responses to surgical stress and to stimulate protein synthesis, and consequently may reduce postoperative complications (57). The ESPEN guideline on clinical nutrition and surgery recommend the use of immunonutrition in the peri- or at least postoperative period, but not exclusively in the preoperative period, in malnourished patients undergoing major cancer surgery (7). However, recently there is reduced confidence in this recommendation (57). A systematic review and meta-analysis published in 2017, including 83 RCTs with 7,116 patients, showed high evidence that the use of immunonutrition after major abdominal surgery had no effect on mortality (58). Immunonutrition reduced overall and infectious complications and shortened length of hospital stay, but the high rate of bias (e.g., reporting, publication, industry-funded) lowers the quality of evidence to low/moderate for these outcomes (58).

Five RCTs have investigated the effectiveness of immunonutrition in patients before and/or after esophageal cancer surgery (59-63). The authors concluded no significant differences on clinical outcomes (e.g., overall complications, infectious complications, hospital stay, weight, QoL) between treatment and control group. More high quality research is needed (58,64) and so far, routine use of immunonutrition in patients undergoing surgery for esophageal cancer is not recommended (15,60).

Alcohol intervention

Alcohol abuse is an independent risk factor for postoperative complications (36,65-67), and this appears to show a dose-response relationship (68). High alcohol consumption (>2 drinks/day, over 28 g ethanol) reduces the immune capacity, cardiac function, increases the endocrine stress response to surgery, reduces blood coagulations and slows down the wound healing process (65,69), all of which are needed for postoperative recovery. A meta-analysis found 3–8 weeks alcohol abstinence before surgery significantly reduced the incidence of wound and cardiopulmonary complications and infections (68). A Cochrane review [2013], including two RCTs, found intensive preoperative alcohol cessation interventions, including pharmacological treatment of alcohol withdrawal, may significantly reduce postoperative complications (66). No effect was found on mortality rates and length of hospital stay (66). In general, more research is needed to clarify the most beneficial timing, duration and intensity of an alcohol cessation intervention program (66). A recent qualitative study found a smoking and alcohol cessation intervention was well received by the participants. Cancer surgery seemed to serve as a kind of refuge and was a useful cue for motivating patients to reconsider the consequences of risky drinking (69,70). Encouraging patients to cease alcohol abuse should be an integral part of preparing for surgery (15,36,69). Alcohol abstinence for at least 4 weeks prior to esophagectomy seems advisable in an enhanced recovery program (15).

Preoperative fasting and carbohydrate treatment

The traditional 'nil per os after midnight' policy prior to elective surgery is not only uncomfortable for patients (7,71,72), but there is also low evidence to support this practice. There is evidence that a minimum fasting period of 2 hours for clear liquids and 6 hours for solids does not increase the risk for aspiration (73). Additionally, prolonged fasting depletes energy reserves (e.g., glycogen, adipose, skeletal tissue) and exacerbates the surgical stress response, which is associated with catabolism, insulin resistance, hyperglycemia, protein muscle loss and prolonged recovery (7,47,71,74,75). In this context, ingestion of an oral carbohydrate solution 2 to 3 hours before surgery is considered as additional intervention to optimize energy reserves and to reduce postoperative insulin resistance (47,76,77), and is nowadays recommended as routine practice in enhanced recovery after surgery programs (7,15,28). An amount of 400 mL of a high-dose (12.5%) carbohydrate solution is recommended (75,76).

These preoperative fasting guidelines, including the use of preoperative carbohydrate drinks, can be applied before esophageal cancer surgery, except in patients with severe dysphagia or other obstructive symptoms. These patients may have an increased risk of aspiration (15,78).

Conclusions

Nutrition care should be an integral part of the multimodal oncology treatment of patients with esophageal cancer to extend survival and to improve QoL. Our focus should move to early detection of malnutrition and cachexia in the preoperative treatment trajectory so that timely and personalized nutrition treatment can be implemented as part of a prehabilitation program. This is key to maximizing patients' chances for a full and rapid recovery from their esophagectomy. Moreover, avoidance of prolonged fasting, using carbohydrate drinks shortly before surgery, and a month of alcohol sobriety prior to surgery also seems to contribute to a faster recovery.

Further research needs to focus on the assessment of body composition for early detection and monitoring of muscle loss in clinical practice and perfecting energy-, protein- and micronutrient requirements in patients with esophageal cancer to determine the best possible nutrition intervention to preserve or improve nutritional status.

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Footnote

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