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Review Article

The Impact of Nutritional Status on the Multimodal Treatment of Oesophageal and Gastric Cancer

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Abstract

The nutritional support of oesophagogastric cancer patients merits attention because of the frequency of these cancers, the high morbidity and mortality rates, and the major impact they have on patient's quality of life. Severe malnutrition in patients undergoing curative treatment of oesophageal and gastric cancers is associated with increased mortality and morbidity, reduced treatment efficacy and increased length of hospital stay. Although no improvement has been determined in relation to cancer survival, both malnourished and non-malnourished patients could benefit from nutritional support during multimodal oncological treatments. This review evaluates the role and impact of nutritional assessment and support for oesophageal and gastric cancer patients undergoing curative treatment.

Keywords: Oesophageal; Gastric; Cancer; Surgery; Chemotherapy; Radiotherapy; Nutrition

Introduction

Oesophageal and gastric cancer have a major impact on patient's nutritional status by virtue of their inherent digestive functions. Many patients with these cancers will require surgical intervention which imposes further metabolic demands and compounds pre-existing nutritional disorders [1,2]. Malnutrition is reported in 60-85% of oesophageal and gastric cancer patients (one of the highest frequencies reported in oncologic conditions), and, a cachexia incidence of 60–80% and 65–85% respectively [3]. Many factors can affect nutritional status, especially disease stage (tumour-related), treatment used (treatment-related), and performance status (patient-related). It is of clinical importance that oesophageal cancer patients who have lost weight will have higher operative mortality and morbidity rates than patients who maintain their weight [4]. Thus routine evaluation of nutritional status will identify the patients at risks of complications and targeted for specific nutritional support. However, trying to maintain an adequate nutritional status is a common problem in oncology, as both the neoplastic disease itself and treatment can lead to malnutrition. These would affect disease progression (morbidity and mortality), therapeutic compliance, quality of life (Qol) and psychological adjustment. Due to decrease in muscle mass and functional capacity (sarcopenia) malnutrition is associated with a poor prognosis [5-7]. There is lower survival, worse response to chemotherapy (CT) and radiotherapy (RT), increased risk of toxicity, increase risk of postoperative complications and nosocomial infections and decreased Qol [8,9]. As a result the approach towards oncological therapy may be forced towards the use of suboptimal and inadequate treatments. Therefore, the possibility of early diagnosis of malnutrition and the inclusion of nutritional intervention into the usual supportive treatment plan is important. However, despite some evidence that it can reduce post-operative infectious complications the role of preoperative nutrition in the form of parenteral nutrition (PN) and enteral nutrition (EN) in improving patient outcome is unclear. A history of rapid onset weight loss may be evidence of advanced disease and not simply due to insufficient nutrient intake or nutrient loss. In addition, malnutrition must be severe to have an effect on surgical outcome [8,10-12]. Without proper study design these confounding factors may render it difficult to demonstrate clearly that improving the nutritional state improves cancer survival.

Oesophagogastric Cancer-Associated Malnutritition

Malnutrition can occur in oesophageal and gastric cancer patients due to increased metabolic demands, insufficient nutrient intake, or nutrient loss. The most common manifestation is tumour cachexia, a complex syndrome that combines malnutrition with weight loss, decrease in muscle tissue (sarcopenia), anorexia, early satiety, weakness, anaemia and oedema [4,5]. The malnutrition related to oesophageal and gastric cancer can be due to: (1) protein-calorie malnutrition or energy deficiency, related to mechanical intake difficulties, disorders of absorption and digestion secondary to cytostatic toxicity and to conditions such as depression- associated anorexia; (2) combined protein-calorie malnutrition, occurring in situations of increased catabolism such as infection or surgical intervention [5,13].

Tumour-related causes of malnutrition

These include mechanical and functional disorders of the digestive system such as dysphagia for oesophageal cancer, and anorexia, early satiety and obstruction for gastric cancer. In addition, metabolic alterations caused by tumour also occur with increased synthesis of positive acute phase protein (C-reactive protein) and catabolism leading to loss of muscle and visceral mass. An increase in lipolysis and circulating triglycerides, and a decrease in lipogenesis and lipoprotein lipase lead to a decrease in adipose mass. Insulin resistance in glucose consumption implies a higher energy cost in the glycolytic pathway [14]. Secretion of cachexia- inducing substances such as cytokines (causing anorexia, weight loss, loss of subcutaneous

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Table 1: Artificial nutrition strategy in oesophageal cancer patients according to the percentage of weight loss.

	Well nourished patients (weight loss <10%)	Malnourished patients (weight loss >10%)
Oral supplementation during neoadjuvant therapy until 1 week preoperatively	Oral supplementation 1 week preoperatively	Perioperatively (1week pre, & 1 week post)
Enteral Nutrition (EN)		
Short-term		*No risk of aspiration*: NGT, *risk of aspiration*: NJT
Long term (>2-3 weeks)		*No risk of aspiration*: PEG before starting neoadjuvant tx, risk of aspiration: PEJ, JET- PEG. Jejunostomy placement at surgery
Parenteral nutrition (PN)		If EN not possible or inadequate

PEG: Percutaneous Endoscopic Gastrostomy; PEJ: Percutaneous Endoscopic Jejunostomy; JET-PEG: Jejunal Extension Tube Through Percutaneous Endoscopic Gastrostomy; NCJ: Needle Catheter Jejunostomy

fat, and sarcopenia) also affects nutritional status [4,5]. Thus, the importance of cachexia as a cause of early death and the elucidation of the relationship between cytokine profile, acute phase response (C-reactive protein level) and resting energy expenditure [5,14].

Patient- related causes of malnutrition

Certain personal habits are directly linked to neoplasia, such as smoking and/or alcohol consumption. Cancer anorexia and cachexia are frequent and serious symptoms of advanced neoplasia. Cancer-related psychological disturbances are often seen in oesophageal and gastric cancer patients (such as fear, anxiety, depression), and these can affect appetite and lead to reduced oral intake [4,5].

Treatment- related causes of malnutrition

Nutritional risk in surgical patients: Surgery may be associated with complications, such as pain, asthenia, anorexia and disorders in digestion processes which interferes with a patient's normal intake patterns [1,4]. Severe malnutrition can have a negative effect on wound healing, predispose to infections, interfere with post-operative adaptation and rehabilitation, and extend hospital stay [5,12]. In general, the surgery-related causes of malnutrition are hyper catabolism, postoperative fasting, prolonged ileus, fistula, malabsorption syndrome, intestinal obstruction and gastric atony [13]. In oesophageal cancer surgery, malnutrition increases the risk of complications such as dehiscences, fistula, mediastinitis and pneumonia [1]. Additionally, oesophageal cancer surgery can cause dysphagia, gastric stasis and malabsorption of fat, leading to steatorrhoea and diarrhea. In gastric cancer surgery, complications such as dehiscences and fistula are less common. However, malabsorption of fat and proteins is quite frequent, as well as limitations in calorie intake due to oesophagitis or dumping syndrome [1,15]. Early satiety is also observed , as well as a decrease in the absorption of iron, calcium, vitamins A, B12, and D (the latter resulting from steatorrhoea) [15].

Nutritional risk in radiotherapy: In general, radiotherapy causes undesirable effects because it affects not only the targeted tumour but also the surrounding tissue. The clinical manifestations of these collateral effects depend on different factors: localization of the tumour, total dose administered fractionation regimens and duration, and existence of concurrent or previous oncology treatments. Manifestations of toxicity can be acute or late, and the side effects can significantly affect the nutritional status of oesophageal and gastric cancer patients. The toxicities intensify if radiotherapy is concomitant with chemotherapy [16]. In oesophageal cancer patients, mucositis, oesophgitis, dysphagia (with or without odynophagia), and/or hypoguesia can cause normal oral intake to be more difficult. These conditions can lead to disturbances in nutritional status, and occasionally force treatment interruption [16,17]. In patients undergoing concurrent chemo and radiotherapy, other factors such as smoking, alcohol consumption, and neutropenia also increase the risk of local infection [18]. In gastric cancer patients, RT can lead to gastritis, nausea, vomiting, food intolerance, anorexia and weight loss [1,3,6].

Nutritional risk in chemotherapy: Chemotherapy affects cellular cycles, particularly in rapidly proliferating cells. It can cause mucositis, enteritis, ulceration and haemorrhages. Malabsorption and diarrhoea can occur and in general, the undesirable effects associated with chemotherapy treatment increase the patient's nutritional risk [3,18].

Nutritional Intervention in Oesophagealand Gastric Cancer Patients

The main objectives of nutritional intervention in an oncology patient are to prevent early death, decrease complications and improve QoL. Nutritional intervention should begin early, and should be part of routine treatment of the cancer patient. A history of weight loss over the preceding 6 months should be sought, and, all patients should have their weight and BMI (in Kg/m^2) measured. Nutrition assessment using a validated nutritional risk tool identifies the at risk patients who are offered dietary advice or considered for pre-operative nutrition. Those with BMI<18.5 or >20% weight loss are of increased risk of post- surgical complication and, hypoalbuminaemia (<30g/l) as a marker of malnutrition is a predictor of adverse surgical outcome [1,11]. There are several possible ways to achieve these goals, but these strategies should be individualized for each patient.

Dietary advice

Dietetic advice should be the first line option as long as oral feeding is possible. This may be sufficient when the patient is capable of consuming at least 75% of their nutritional requirement to maintain good health and there is no radiotherapy, chemotherapy, or surgery programmed [1,5]. As smaller volumes of meals are tolerated best, food with high nutritional content should be presented in small quantities with consideration of the patient's preference to the presentation and preparation. Dietary recommendations are intended to control the symptoms of anorexia, dysphagia (modification of food consistency) and mucositis (soft and smooth foods with optimum oral hygiene). The pain of mucositis is prevented, the oral dryness caused by a decrease and modification of saliva production is alleviated and flavor of the food improved. A personalized dietetic advice and oral supplementation can increase dietary intake, help prevent weight loss associated with cancer treatment and the unplanned interruption

Table 2: Artificial nutrition strategy in gastric cancer patients according to the percentage of weight loss.

	Well nourished patients (weight loss <10%)	Malnourished patients (weight loss >10%)
Oral supplementation during neoadjuvant therapy until 1 week preoperatively	Oral supplementation 1 week preoperatively;	Perioperatively (1 week preoperatively & 1 week postoperatively)
Enteral Nutrition (EN)		
Short-term		
Long term (>2-3 weeks)	Tube feeding to prevent postoperative weight loss (i.e. to support patients during adjuvant therapy).	Jejunostomy placement at staging laparoscopy or nasojejunal tube (NJT) feeding (gastrostomy contraindicated). Tube feeding to prevent postoperative weight loss (i.e. to support patients during adjuvant therapy).
Parenteral nutrition (PN)		If EN not possible or inadequate

of radiotherapy [5,19]. When dietetic advice is insufficient or malnourished patients with inadequate intake for more than 5 days, a higher level of nutritional support is initiated for 10-14 days. Optimal duration for artificial nutrition seems to be at least 7 days [20].

Artificial nutrition as perioperative nutritional support

Requirements and intakes: Energy (caloric) needs are about 30kcal/kg/day in patients confined to bed and 35Kcal/Kg/day in ambulatory patients. In the postoperative period, artificial nutrition is required for patients who are unable to achieve 60% of their requirements [1,7,19,21]. Energy sources are provided by glucides (50-70%) and lipids (30-50%). Nitrogen requirements vary from 0.15 to 0.2 g/kg/day during the pre-operative period to 0.25 to 0.30 g/kg/day during the post-operative period. Glucidic needs are usually covered with an intake of 3 to 4 g/Kg/day. Lipid requirements vary from 1.5 to 2 g/kg/day, not exceeding 2g/kg/day. Daily intake of phosphorous, magnesium, vitamins and trace elements must be ensured, and electrolyte intakes (KCL and NaCL) should be adapted to estimated requirements based on blood values [21]. Short course of preoperative nutritional support (<7 days) are entirely ineffective [7].

Indications for perioperative nutritional support: During the perioperative period, artificial nutrition is not required in well-nourished patients, or those with weight loss of <10%, who can consume at least 60% of their requirements via an oral diet within the week following surgery. Preoperative artificial nutrition is recommended in severely malnourished patients with weight loss >20% who will benefit from major surgery. Where possible this should be provided by the enteral route [1,7]. The same approach may be useful for patients with moderate malnutrition (weight loss between 10% and 19%). Postoperative artificial nutrition is recommended in (a) all patients who benefited from preoperative artificial nutrition, (b) in all malnourished patients, (c) in all patients who have no possibility for an oral diet in the postoperative period, or can only consume <60% of their requirements via an oral diet within the week following surgery [1,19,21].

Route of administration: Oral supplementation should be used when the patient is unable to consume more than 50 to 75% of their requirements by means of conventional feeding for a period longer than five consecutive days, or in cases of malnutrition. Enteral tube feeding should be used when the patient is unable to consume at least 50% of their requirements by means of conventional feeding for a period longer than five consecutive days, or in cases of moderate or severe malnutrition [22-24]. Enteral nutrition is recommended when the gastrointestinal tract is functional, as it has superior efficacy, lower morbidity rates and lower costs compared with parenteral nutrition [20,22-26]. In cases were swallowing is affected (as in oesophageal cancer) or if serious mucositis is expected, intragastric feeding through nasogastric tube (if no risk of aspiration) or nasoenteric/jejunal tube (if risk of aspiration) for a duration of less than 2 to 3 weeks (short-term); or through a gastrostomy in oesophageal cancer, and a jejunostomy in gastric cancer for long-term (>2-3 weeks) feeding is recommended [1,21]. When there is no risk of aspiration in oesophageal cancer, percutaneous endoscopic gastrostomy (PEG) is useful for long-term feeding, but with a risk of aspiration a percutaneous endoscopic jejunostomy (PEJ) or the jejunal extension tube through percutaneous endoscopic gastrostomy (JET-PEG) is utilized. Generally, PEG in patients scheduled for gastric pull-up is controversial and rejected by many surgeons [27]. The feeding needle catheter jejunostomy (NCJ) tube can be inserted during laparoscopic staging of gastric cancer or at surgery. After oesophageal and gastric cancer surgery enteral nutrition should be started distal to the anastomosis [21]. It is advisable to begin enteral nutrition as a continuous feed at a low flow rate (10-20 ml/h) and increase the flow rate depending on the degree of tolerance and particular position of each patient until the target intake is reached [21]. Early postoperative enteral nutrition significantly decreases the postoperative infectious complication rate and length of hospital stay when compared with parenteral nutrition, but is associated with a decreased tolerance rate [20]. The parenteral route is used when enteral nutrition is contraindicated, or intake is inadequate to fulfill the patient's caloric requirements. It is reserved for those patients for which enteral nutrition is indicated but not possible due to a non-functional or inaccessible gut [1,28]. Parenteral nutrition does not modify postoperative mortality [26] but decreases postoperative infectious mortality [24,26].

Artificial nutrition for oesophageal and gastric cancer patients undergoing radiotherapy and chemotherapy: Patients with malnutrition have more difficulty overcoming complications that may derive from surgery, radiotherapy and chemotherapy regimens, with an increase in adverse effects [6,7,18]. Nutritional support will ensure the patient is optimally prepared, and even in the face of complications, is associated with minimal depletion of body stores. The chemotherapy and radiotherapy side effects including dysphagia, mucositis, sore mouth, nausea, and diarrhea can impinge on appetite and dietary intake. There is no evidence that artificial nutrition affects tumour growth nor does have any effect on treatment response or side effects of radio or chemotherapy [1,6,18]. The aim is to maintain weight and nutritional status so as to reduce the effect of malignancy and therapy (Table 1 and 2). In patients who are losing weight because of insufficient intake, prolonged oral supplementation or retention of

feeding adjuncts, such as jejunostomy tubes is vital in improving and maintaining nutritional status [1,18]. In patients with oesophageal cancer, enteral nutrition via tube (nasogastric tube/nasojejunal tube) may be more appropriate than oral feeding, particularly if dysphagia is present or serious mucositis is expected during treatment. In patients undergoing adjuvant radiotherapy and/or chemotherapy, nutritional support could be achieved via feeding tube access either transnasally (NGT/ NJT) or by percutaneous ostomies (PEG/PEJ) [1,7,11,19,26]. Although standard formulas should be used in enteral nutrition, formulas enriched with omega -3 fatty acids may have a positive effect on cachexia. The results are, however, controversial regarding their effect on improving nutritional status or general state. In addition, no improvement in cancer survival has been determined [26]. Removable stents such as polyflex should be considered in patients with persistent dysphagia [21].

Complications: Although feeding tubes are intended for long-term, problem-free enteral access, complications of enteral feeding are (1) related to intubation of gastrointestinal tract (fistulation, wound infection, peritonitis displacement and catheter migration (including small bowel obstruction), blockage of tube) and (2) related to delivery of nutrient to gastrointestinal tract (aspiration and hospital-acquired pneumonia (especially if feed contaminated), feed intolerance and diarrhea). The metabolic complications that may occur include hyperglycaemia, hypokalaemia, water and electrolyte imbalance, hypophosphotaemia, and hypomagnesaemia [29]. These complications are secondary to inadequate selection of nutrition according to a patient's clinical and nutritional status, to inadequate management of the enteral feed, and to suboptimal clinical care [20,30]. The major complications associated with the provision of parenteral nutrition are related to the central venous catheter (mechanical, infectious and thromboembolic). The mechanical complications include blockage, central vein thrombosis, migration, fracture and dislodgement. The infective complications include exit site infection, line sepsis and infective endocarditis. In addition, prophylactic preoperative parenteral nutrition has been shown to increase the operative morbidity, especially in patients with only mild-moderate malnutrition and increase iatrogenic infectious morbidity in well-nourished patients [21]. The metabolic complications include hyper or hypoglycaemia, deranged liver function related to biliary stasis and excessive calorie administration with fat deposition in liver, hypertriglyceridaemia from too much lipid infusion and hyperchloraemic acidosis from too much chloride in nutrient solution [20,21]. On the background of these complications, it is reasonable to suggest that malnourished patients (>10% weight loss) should, if possible, be offered preoperative nutritional support but this should be provided by the enteral route where possible.

Immunonutrition: Major surgery leads to a decline in immune status, and consequent increases in postoperative mortality and infectious morbidity rates [14,31]. Enhancing immune function may lead to a decrease in such complications. Enteral immunonutrition (EIN) has been increasingly used to enhance host immunity and relieve inflammatory response of patients undergoing surgery for GC. Wong et al. [32] demonstrated that immune- enhancing enteral nutrition decreased wound infection rates and reduced length of hospital stay and recommended its inclusion as part of the Enhanced Recovery after Surgery (ERAS) programmes for upper GI Surgery. The most frequently used immunonutrition products consist of a combination of arginine, glutamine, polyunsaturated omega-3 fatty acids, nucleotides and antioxidant micronutrients (vitamin E, vitamin C, beta-carotene, zinc and selenium). The administration route is either parenteral (glutamine), enteral or oral. Immunonutrition is more effective than a standard diet with the same energy and nitrogen balance when prescribed in the postoperative setting. Reductions in length of hospital stay and costs favour immunonutrition, regardless of the patient's nutritional status [33-36]. Enteral immunonutrition lasting 7 days is recommended in the preoperative setting in all patients who will benefit from oncological gastrointestinal surgery. In the postoperative period immunonutrition is continued in all patients who were malnourished in the preoperative period for 7 days in the absence of postoperative complications or until patients can consume an oral diet meeting at least 60% of their requirements. In malnourished patients (weight loss >10%), preoperative nutrition alone is less effective than perioperative immunonutrition, but in all cases perioperative immunonutrition is more efficient than standard enteral nutrition. Preoperative immunonutrition decreases rates of postoperative infectious complications and length of hospital stay, but has no significant effect on postoperative mortality [35]. In well- nourished patients (weight loss <10%), preoperative immunonutrition lasting 5 to 7 days decreases the incidence of postoperative infectious complications as well as the length of hospital stay [36]. However, conclusions across studies still remain unclear [37,38]. Recent meta-analyses of randomised controlled trials comparing the clinical benefits of standard enteral nutrition with those of enteral nutrition supplemented with a variety of immune-modulating substances failed to demonstrate consistent differences in patients' postoperative clinical course, complications, length of hospital stay and inflammatory marker levels on gastrectomy and oesophagectomy patients [37,38].

Conclusions

Nutritional support should be included as a strong therapeutic weapon during active oncological treatments. The main objectives are to prevent early death, decrease complications and improve quality of life. Although, there is some evidence that improving nutritional status reduce complications the role of preoperative nutrition in improving patient outcome is unclear. Disadvantages of preoperative parenteral nutrition include major complications and increased cost of treatment. Feeding jejunostomy inserted during a staging laparoscopy for gastric cancer or at surgery for both oesophageal and gastric cancer would prevent postoperative weight loss and support the patient during adjuvant therapy, but there is mounting evidence of complications with prolonged jejunal feeding. Enteral access services should thus be able to manage the complications related to feeding tubes. Oral nutritional supplements (immunonutrition) are cheaper and easier to administer than parenteral or enteral nutrition, and have few disadvantages. Perioperative immunonutrition in all cases is more efficient than standard nutrition although the evidence on postoperative outcome is not so strong in all patients undergoing oesophageal or gastric resection for cancer.

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