

# Nutritional Status in Patients with Esophageal Cancer

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Esophageal cancer is associated with shorter survival times due to the increased incidence of malnourishment and cachexia in patients with the disease, which is prevalent in patients with obesity, as well. Although the prognostic significance of the nutritional status does not mean exclusion from treatment, the need for timely nutritional assessment is important, as interventions for the treatment of malnutrition can considerably improve survival.

nutritional assessment

esophageal cancer

nutritional status

## 1. Introduction

Malnourishment constitutes a frequent finding in patients with cancer, even at the time of diagnosis. Malnourishment prevalence ranges from 31% to 87% and depends on the tumor's histopathological stage and type, medication, and the personalized characteristics of each patient <sup>[1][2]</sup>. Body weight decline commonly arises due to enhanced energetic requests, low energetic intake, and/or the existence of nutrient malabsorption. In carcinoma patients, undereating could be ascribed to several causes. Inflammation and catabolism related to tumor development and progression may also result in atrophy of muscles, underweight, and sarcopenia, while cancer gastrointestinal blockage may diminish food consumption and may lead to malabsorption. In particular, swallowing difficulties, aches, and nausea could be triggered <sup>[3][4]</sup>. In addition, cancer treatment may result in several adverse side effects, including low appetite, early satiety, nausea, sickness, oral and intestine mucositis with low swallowing disturbances, diarrhea, hemorrhoids, and anal fissures; alterations in smelling and tasting disturb not merely the whole energetic increase, but also the increased risk of nutrient malabsorption, negatively affecting nutritional status <sup>[4]</sup>. The presence of cognitive impairments in cancer patients is also able to influence their capability to take energy by food consumption <sup>[4]</sup>.

Malnourishment in esophageal cancer is a common and serious concern, with dysphagia severely impairing patients' nutritional status <sup>[5]</sup>. Malnutrition also increases the probability of low compliance to medication therapy and radiotherapy and, finally, adverse disease outcomes <sup>[6][7][8]</sup>. Cancers of the esophagus and the pharynx can impair feeding in patients and lead to undernutrition <sup>[6][7][8]</sup>. Nutrition impact symptoms negatively influence cancer patients beyond the acute phase of cancer therapy <sup>[9][10][11]</sup>. These symptoms are linked with reduced nutrition and quality of life. Notably, 23.8–48.9% of patients with oral cancers are diagnosed with malnutrition <sup>[9][10]</sup>, while the rates for esophageal cancer patients reach 79% <sup>[8]</sup>.

Nutritional assessment is important in order to prevent and manage malnutrition [10], whilst nutritional status acts as a prognostic factor for disease progression [12]. A substantial concern regarding malnutrition is underdiagnosis [13], even if nutritional assessment testing is recommended to be accomplished during the diagnostic procedure [11]. Moreover, analyzing body composition can decrease the likelihood of medication toxicity, can be favorable for prognosis, reduce disease development, decrease the risk of complications due to surgery, improve performance status, and increase survival times [14]. In contrast, BMI alone cannot differentiate fat mass from fat-free mass and is not representative of body-weight decline [15].

## 2. Nutritional Status in Patients with Esophageal Cancer

Esophageal cancer is associated with shorter survival times due to the increased incidence of malnourishment and cachexia in patients with the disease [16], which is prevalent in patients with obesity, as well [17]. Although the prognostic significance of the nutritional status does not mean exclusion from treatment [18], the need for timely nutritional assessment is important, as interventions for the treatment of malnutrition can considerably improve survival [19]. There are adequate, validated questionnaires that evaluate nourishing state, which have been applied in several studies, and shown prognostic potential [20][21]. In fact, Wang et al. performed a prospective study in 192 patients with esophageal carcinomas and found that both the Geriatric Nutritional Risk Index (GNRI) < 92 and the European Society of Clinical Nutrition and Metabolism (ESPEN 2015) 2015, two malnutrition diagnosis reference tools, showed good property in predicting major complications, infectious complications, overall complications, and delayed hospital discharge [20]. By performing a retrospective analysis of 155 esophageal cancer patients, they also confirmed the better performance of GNRI < 92 in predicting perioperative morbidities than the other three nutritional indexes [20]. In a retrospective study, 340 esophageal squamous cell carcinoma patients who completed curative treatment and received a nutrition evaluation by the Patient-Generated Subjective Global Assessment (PGSGA) score; malnutrition (patients with a high PGSGA score) was associated with advanced stage and reduced survival rate [21]. Surgical resection brought the survival benefit to patients in the low PGSGA group, but not for the malnourished patients after neoadjuvant treatment [21].

A plethora of recent surveys have explored the potential importance of “Controlling Nutritional Status” (CONUT) scoring in patients’ survival of esophageal carcinoma. These studies showed that CONUT scoring may be a significant prognosticator of overall and disease-specific survival in patients who have undergone esophagectomy [22]. More to the point, a systematic literature review was carried out to investigate the impact of the CONUT score in esophageal cancer, including five studies with 952 patients [22]. This meta-analysis found a significant association of the CONUT score with outcomes including overall survival, cancer-specific survival, and recurrence-free survival [22]. Moreover, in a recent retrospective survey of 69 individuals with progressed esophageal cancer receiving treatment with an immune checkpoint suppressor, the CONUT score was independently associated with overall and progression-free patient survival [23]. In addition, among patients treated with an immune checkpoint inhibitor, a high CONUT score was associated with significantly worse progression-free survival (PFS) and overall survival compared with a low CONUT group [23]. A retrospective survey by Hirahara et al. (2018) conducted on 148 consecutive patients who underwent potentially curative surgery for histologically verified esophageal squamous

cell carcinoma also confirmed that the CONUT scoring was independently associated with cancer-specific survival in patients aged < 70 years old who undergo curative surgery [24]. Further retrospective studies highlight that the CONUT score can predict malnutrition and act as a prognosticator of overall and disease-specific survival in patients treated with surgery [25][26]. A retrospective study was performed on 352 patients who had undergone elective esophagectomy with lymphadenectomy for esophageal cancer and were assigned to three groupings based on the CONUT assessment [25]. Malnourished patients exhibited a considerably elevated prevalence of any morbidity, serious morbidities, and surgical site infections. Hospitalization of malnourished patients was found substantially extended. In a multivariate analysis, intermediate or advanced malnourishment was independently associated with the probability of any morbidity and serious morbidities [25]. Another retrospective study by the same research group was conducted on 373 patients who had undergone three-incision esophagectomy with two- or three-field lymphadenectomies due to esophageal carcinoma [26]. This study showed that malnourished patients underwent a considerably elevated incidence of reoperation and a greater tendency of lung morbidities [26]. CONUT score was able to predict malnutrition and acted as a prognosticator of overall and disease-specific patient survival [26]. Regarding recurrence, a recent retrospective study using the CONUT score, with a cut-off point of three, found that patients who underwent neoadjuvant immunochemotherapy with high CONUT were more likely to relapse, while those with a reduced CONUT scoring exhibited a favorable disease-free survival after one year [27]. Moreover, vessel invasion, postoperative pneumonia, and advanced ypT, cTNM, and ypTNM stages were substantially related to patients scoring high CONUT values [27].

The Prognostic Nutritional Index (PNI) score has been applied in a few recent studies with esophageal carcinoma patients. In fact, PNI was used in a study group of 337 patients, and those with a low PNI (<45) had shorter overall survival than those with a high PNI score [28]. Interestingly, PNI was considerably related to tumor-infiltrating lymphocytes (TILs) state and CD8-positive cell count, supporting evidence that nutritional status and systemic immune competency could affect patient survival via local immune response [28]. A recent study on 407 patients who underwent curative esophagectomy indicated that a reduced PNI score < 48.33 was independently associated with overall survival, being also associated with a high prevalence of postoperative complications [29]. A smaller study with 32 individuals with esophageal squamous cell cancer who experienced salvage esophagectomy showed that PNI, with a cut-off point of 45, was identified as an independent preoperative prognosticator for overall survival [30]. After adjustment for patient age, clinical response, and preoperative PNI, PNI was not a prognosticator for disease-specific survival [30]. Nakatani et al. (2017) investigated the potential of PNI to predict prognosis in 66 individuals who had undergone neoadjuvant chemotherapy and applied as a cut-off point the PNI score of 45, like the aforementioned studies [31]. Preoperative PNI was independently associated with shorter overall and relapse-free survival, yet prechemotherapy PNI was not independently correlated with overall and relapse-free survival [31]. Wang et al. (2018) showed that PNI was independently associated with overall survival, but not with progression-free survival, organ metastasis-free survival, and local regional relapse-free survival [32]. Concerning patients at risk of malnutrition, the average days of patients staying in the hospital for nutritional support were significantly shorter, and the mean costs of staying in the hospital were smaller than those without nourishing care [32].

The Patient-Generated Subjective Global Assessment (PG-SGA) is another diagnostic questionnaire that has been explored in individuals with esophageal cancer. Movahed et al. (2020) followed up 71 newly diagnosed patients for

one year [33]. At the end of the first year, mortality was related to decreased BMI prior to chemoradiotherapy, baseline PG-SGA scoring, weight decline, low BMI ( $<18.5 \text{ kg/m}^2$ ), and decreased mid-upper arm circumference (MUAC) [33]. The twelve-month mortality was significantly associated with lower BMI after chemoradiotherapy, primary PG-SGA score, weight loss, BMI  $< 18.5$ , MUAC, physical performance, living in rural or urban areas, and addiction [33]. Furthermore, Chen et al. (2021) performed a study on 620 newly diagnosed patients with esophageal squamous cell cancer at stages T2 to T4 or regional lymph node metastasis. This study used five nutritional parameters: serum albumin, (BM), GNRI, prognostic nutritional index (PNI), and a new modified nutritional risk index (mNRI). All nutritional parameters were significantly correlated with tumor length and pT category. Decreased nutritional parameters were significantly correlated with poor survival in univariate analysis; however, only the mNRI was an independent prognostic factor in multivariate analysis [34]. A meta-analysis study including 15 studies and enrolling 1864 participants found that preoperative nutrition could reduce infectious complications and length of hospital stay after esophagectomy, whereas no significant difference was revealed in the incidence of overall complications in-hospital mortality, and anastomotic leak [35]. This study supported evidence that preoperative nutrition is safe in esophageal cancer; however, potential benefits can be observed in infectious complication rate and length of stay on a limited scale [35]. It is important to note that cut-off points may differ in different studies, which may confuse clinicians [33][34][35].

As far as short-term outcomes and complications are concerned, further studies have been undertaken. A retrospective study was performed on 100 patients with esophageal cancer who were treated with definitive chemoradiotherapy, preoperative chemoradiation, and definitive radiotherapy [36]; 44% of the enrolled patients with a PG-SGA score  $\geq 9$  at baseline showed severe malnutrition, and 41% of patients developed grade  $\geq 2$  radiation esophagitis [36]. Multivariate analysis revealed that PG-SGA score  $\geq 9$  ( $p = 0.042$ ) was the independent predictor of radiation esophagitis [36]. Regarding postoperative complications, studies have shown that greater body weight loss, low albumin levels, and low GNRI were predictors for major complications [37], while high NRS-2002 score [38] and low PNI [29] were also associated with frequent postoperative complications. In fact, in the study of Lidoriki et al., 52.9% of the patients developed postoperative complications and both albumin and GNRI levels were lower in patients who developed major complications compared to patients who did not develop postoperative complications [37]. Major complications were associated with a higher percentage of weight loss and with low handgrip strength, while albumin and low muscle mass were significantly associated with anastomotic leakage occurrence [37]. Furthermore, Hikage et al. (2019) retrospectively evaluated 141 esophageal cancer patients who were treated with neoadjuvant chemotherapy postradical esophagectomy and found that, based on the CONU score, malnutrition occurred only from 14 days after surgery in most cases. According to PNI, the ratio of malnutrition increased gradually from presurgery to 14 days after surgery [39]. A multivariable analysis of independent prognostic factors predicting survival identified malnutrition 14 days after surgery with the CONUT score and a low PNI before surgery, invasion depth of the primary lesion, and node metastasis. [39]. Further studies have also highlighted the prognostic value of CONUT for short-term postoperative complications after esophagectomy [25][40]. Notably, in the study of Horinouchi et al., a total of 674 patients who underwent esophagectomy (296) and minimally invasive esophagectomy (378) were analyzed [40]; 32 patients of the esophagectomy group and 16 of the minimally invasive esophagectomy group were classified as having moderate

and severe malnutrition, respectively. Moderate and severe malnutrition was significantly associated with a low BMI, poor performance status, poor American Society of Anesthesiologists physical status, advanced cancer stage, and frequent preoperative treatment [40]. These patients also showed considerably more frequent morbidities of grade  $\geq$  IIIb based on the Clavien–Dindo classification (CDc), respiratory, and cardiovascular morbidities after esophagectomy [40]. Moreover, moderate and severe malnutrition in CONUT was an independent risk factor for morbidity of CDc  $\geq$  IIIb, respiratory, and cardiovascular morbidities [40]. Thus, preoperative malnutrition in CONUT reflected diverse disadvantageous clinical factors and may be considered a predictor of worse short-term outcomes after esophagectomy; however, it had no value in minimally invasive esophagectomy [40].

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