

Handgrip Strength Is Associated With Treatment Modifications During Neoadjuvant Chemoradiation in Patients With Esophageal Cancer

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Abstract

Rationale: It has been shown that early nutrition intervention improves nutrition status (NS) and treatment tolerance in patients with esophageal cancer. However, it remains unknown whether pretreatment parameters of NS are associated with treatment modifications (TMs) during neoadjuvant chemoradiation (CR) in patients who are intensively nutritionally supervised during treatment. **Methods:** All outpatients with esophageal cancer who were scheduled for CR in the VU medical center from 2006–2015 were included. NS was assessed by body mass index (BMI), weight loss in the past 6 months (WL), fat mass index (FMI) and fat-free mass index (FFMI), handgrip strength (HGS), and energy/protein intake. Logistic regression analyses, adjusted for age, sex, previous tumor, tumor stage, and physical status, were applied. TMs were defined as delay, dose reduction or discontinuation of chemotherapy and/or radiotherapy, hospitalization, or mortality (yes/no). **Results:** In total, 162 patients were included (73% male; mean age 65 ± 9 years). Mean BMI was 25.1 ± 4.5 kg/m², and WL was 4.8 ± 5.1 kg. HGS and FFMI were below the 10th percentile of reference values in 21 and 37 patients, respectively. Thirty-five (22%) patients experienced at least 1 TM during CR; unplanned hospitalization (n = 18, 11%) was the most prevalent. After adjustments for confounders, only HGS was statistically significantly associated with TMs (odds ratio, 0.93; 95% confidence interval, 0.88–1.00). **Conclusion:** In this group of intensively supervised patients with esophageal cancer, pretreatment parameters of NS had little influence on TMs during CR. Only a lower HGS was associated with TMs. (*Nutr Clin Pract.* XXXX;xx:xx-xx)

Keywords

esophageal cancer; nutrition status; malnutrition; chemoradiotherapy

Malnutrition is a frequently observed phenomenon in patients with esophageal cancer, with a reported prevalence of up to 60%–85%.^{1,2} In patients with cancer, it is well known that malnutrition negatively affects response to therapy and increases side effects.^{3,4} Currently, curative treatment for esophageal cancer consists of 5.5 weeks of neoadjuvant chemoradiation, followed by esophagectomy.^{5,6} Both the disease itself and the therapy may account for the high prevalence rates of malnutrition in patients with esophageal cancer.^{7,8}

It has long been known that unintentional weight loss is associated with more frequent side effects in patients with gastrointestinal (GI) cancer,^{9,10} whereas early nutrition intervention has been shown to improve clinical outcomes such as nutrition status, number of unplanned hospital admissions, and tolerance of the planned chemoradiation.^{11,12} Therefore, all patients treated with neoadjuvant chemoradiation for esophageal cancer at our medical center currently receive individualized nutrition intervention throughout their complete treatment trajectory.

In previous studies, a poor nutrition status in patients with GI cancer at the start of treatment has been associated with a lower response to chemotherapy and radiotherapy and with an

increase of adverse events during treatment.^{8,13} However, it is unknown whether pretreatment parameters of (an abnormal) nutrition status such as handgrip strength (HGS), pretreatment weight changes, or fat-free mass index (FFMI) are associated with increased occurrences of treatment modifications, even

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when patients receive intensive individualized nutrition counseling during treatment. Therefore, the aim of this study is to assess the association between the different parameters of nutrition status before the start of chemoradiation and treatment modifications during neoadjuvant chemoradiation in patients with esophageal cancer who are intensively nutritionally supervised during treatment.

Methods

Study Population and Study Design

All consecutive outpatients with esophageal cancer who were scheduled for neoadjuvant chemoradiation from 2006–2015 at our medical center were included. Chemoradiation consists of 5 weekly cycles of chemotherapy of intravenous (IV) cisplatin and IV paclitaxel and concurrent radiotherapy, given in 23 fractions on 5 days per week, before surgery.¹⁴ All patients fulfilling this treatment schedule were included; therefore, there were no exclusion criteria. As part of routine nutrition and medical workup, patient characteristics and data on nutrition status were prospectively collected before the start of the neoadjuvant chemoradiation. These prospectively collected data were retrospectively completed with data on the course of chemoradiation from medical charts. This study was approved by the Medical Ethic Review Committee. Informed consent was waived as data were collected as part of routine patient care.

Patient characteristics

Anthropometry. Current body weight was measured on a calibrated scale to the nearest 0.1 kg, and body weight history was inquired or obtained from medical charts. Height was measured to the nearest 0.1 cm standing upright or inquired. Body mass index (BMI) was obtained from current weight divided by height² (kg/m²).

Physical status and tumor stage. Physical status was scored using the American Society of Anesthesiologists (ASA) score, a grading system for preoperative functional health. This system is based on 5 classes, with higher scores indicating worse physical status. In general, only patients with a score ≤ 3 are considered for surgery.^{15,16} Data of previous tumor(s) and tumor stage were obtained from the medical charts. Tumor stage was scored using the American Joint Committee on Cancer (AJCC) stage system.¹⁷

Baseline Nutrition Status

The following baseline parameters of nutrition status were determined: FFMI, fat mass index (FMI), recent weight loss and weight loss over the past 6 months, BMI, protein and energy intake, and HGS. A registered dietitian performed a nutrition assessment 1–2 weeks before the start of neoadjuvant chemoradiation.

Body composition was determined using bioelectric impedance analysis (BIA) (Body Stat 1500; Euromedix, Leuven, Belgium), preferably on the right side of the body and with an empty bladder. Fat mass (FM) and fat-free mass (FFM) were calculated from resistance and reactance using the Kyle et al¹⁸ equation. FFMI was calculated as FFM divided by height² (kg/m²), whereby values below the 10th percentile were considered too low.¹⁸ HGS was measured with a handheld dynamometer (hydraulic or digital JAMAR; Patterson Medical, Bolingbrook, IL). The test was performed sitting, and patients were instructed to perform 3 consecutive contractions with their nondominant hand. The mean value was compared with reference values from Bohannon et al,¹⁹ whereby values below the 10th percentile were considered too low. Patients were classified malnourished if they fulfilled the criteria of the new European Society for Clinical Nutrition and Metabolism (ESPEN) definition for malnutrition. This definition consists of the following criteria: BMI <18.5 kg/m² to define malnutrition and the combined finding of unintentional weight loss (mandatory) and either reduced BMI or FFMI. Weight loss could be either $>10\%$ of habitual weight indefinite of time or $>5\%$ over 3 months. Reduced BMI is <20 or <22 kg/m² in patients younger and older than 70 years, respectively. Low FFMI is <15 and <17 kg/m² in females and males, respectively.²⁰

A 24-hour diet recall and global diet history were obtained by a registered dietitian. The 24-hour recall is a valid method to measure the intake over the past 24 hours; the dietary history completes this method with data on more habitual intake. The combined method is feasible within the limited time for dietetic consultation in clinical practice.²¹ All patients received individualized nutrition counseling, aimed at meeting their nutrition requirements during neoadjuvant chemoradiation. Energy requirements were calculated using the Harris-Benedict equation (2006–2012) or the World Health Organization (WHO) equation (2013–2015), multiplied by 1.3–1.5: 30% extra for physical activities and, if necessary, an additional 20% for weight gain. For protein goals, the requirements were determined at 1.2–1.5 g/kg/d, corrected for underweight or overweight (BMI <18.5 to BMI = 20 and BMI >30 to BMI = 27.5).^{22,23} Energy and protein intakes were calculated as a percentage of requirements. If deemed necessary by the dietitian, additional sip and/or tube feeding was started.

Treatment Modifications

Primary outcomes of this study were treatment modifications during neoadjuvant chemoradiation, defined by at least one of the following modifications: delay (>1 week), dose reduction or discontinuation of chemotherapy and/or radiotherapy, hospitalization, or mortality. These variables were dichotomized (yes/no). If one of the treatment modifications occurred during neoadjuvant chemoradiation, the interpretation of the overall outcome variable was “yes.”

Statistical Analysis

Data are presented as mean and standard deviation (SD) for normally distributed data or median \pm interquartile range if not normally distributed. Univariate logistics regression analyses were used to examine the associations between the different parameters of nutrition status as continuous parameters and treatment modifications (yes/no). All analyses were a priori adjusted for age and sex (model 1) and also for the following confounders: previous tumor (yes/no), tumor stage (yes/no), and ASA score (model 2). For the interpretation of the results, a *P* value $< .05$ was considered to indicate statistical significance. Statistical analyses were performed in SPSS version 22 (SPSS, Inc, an IBM Company, Chicago, IL).

Transparency Declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from this study as planned (and registered with) have been explained. The reporting of this work is compliant with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Results

Patient Characteristics

Table 1 shows a summary of the baseline characteristics of the 162 patients included. Mean age was 65 ± 9 years, and 73% were male. Stages II and IIIA were the most prevalent tumor stages ($n = 46$ [30%] and $n = 57$ [37%]). Mean BMI was 25.1 ± 4.5 kg/m². Fifty-three patients (33%) had lost $>5\%$ of their preillness weight in the 6 months prior to diagnosis. Based on the new ESPEN malnutrition criteria, 20 patients (12%) were malnourished.²⁰ Twenty-nine patients (18%) had an HGS below the 10th percentile, and 43 patients (36%) had a FFMI below the 10th percentile. At their first consultation, 90 patients (65%) met their calculated energy requirements, 26 patients (19%) met their calculated protein requirements, and 22 patients (14%) met their calculated energy and protein requirements. In 69 patients (43%), sip and/or enteral feeding was initiated before the start of neoadjuvant chemoradiation.

Treatment Modifications

Thirty-five patients (22%) experienced at least 1 treatment modification during neoadjuvant chemoradiation (Table 2), and 9 patients (6%) experienced 2 or more treatment modifications. Unplanned hospitalization ($n = 18$, 11%) was the most frequently observed modification, followed by dose reduction of chemotherapy ($n = 15$, 9%) and delay of neoadjuvant

Table 1. Baseline Characteristics of Patients With Esophageal Cancer Treated With Neoadjuvant Chemoradiation (N = 162).^a

Characteristic	Total No.	Value
Sociodemographics		
Sex, No. (%)	162	
Male		118 (73)
Female		44 (27)
Age, y	162	65 ± 9
Anthropometry		
Height, cm	162	176 ± 9
Weight, kg	159	77.9 ± 15.9
Male		80.6 ± 14.4
Female		70.6 ± 17.6
BMI, kg/m ²	159	25.1 ± 4.5
Weight loss last 6 months, kg	115	4.8 ± 5.1
Weight loss 1 month, kg	112	1.4 ± 5.4
$>5\%$ weight loss last 6 months, No. (%)	115	53 (33)
Tumor characteristics		
Previous tumor, No. (%)	162	26 (16)
Stage grouping, No. (%)	154	
I		17 (11)
II		46 (30)
IIIA		57 (37)
IIIB		17 (11)
IIIC		17 (11)
Not detectable		8 (5)
Physical status		
ASA, No. (%)	155	
I		14 (9)
II		99 (64)
III		37 (24)
IV		4 (3)
Nutrition assessment		
Handgrip strength, kg	114	35.5 ± 11.6
Male		39.8 ± 9.7
Female		25.5 ± 9.4
$<P10$, ^b No. (%)		29 (18)
FFM, ^c kg	120	53.9 [48.0; 62.0]
Male		58.5 [54.0; 64.0]
Female		40.5 [36.5; 48.0]
FFMI, kg/m ²	120	17.4 ± 3.3
Male		18.2 ± 2.9
Female		15.4 ± 3.2
$<P10$, ^d No. (%)		43 (36)
Energy intake vs requirement, %	139	65.3 ± 21.7
Protein intake vs requirement, %	138	66.2 ± 21.3
<1.2 g/kg/d, %		66.0
1.2 – 1.5 g/kg/d, %		13.6
>1.5 g/kg/d, %		5.6

ASA, American Society of Anesthesiologists; BMI, body mass index; FFM, fat-free mass; FFMI, fat-free mass index.

^aValues are presented as mean \pm SD unless indicated otherwise.

^bCutoff points handgrip strength ($<P10$): men >65 years: right = 37.6 kg, left = 34.2 kg; women >65 years: right = 23.6 kg, left = 20.7 kg.⁷

^cCut of point FFM ($<P10$): men >65 years = 50.4 kg; women >65 years = 35.7 kg.

^dCut of point FFMI ($<P10$): men >65 years = 17.6 kg; women >65 years = 14.6 kg.⁶

chemoradiation with >1 week ($n = 13$, 8%). None of the patients died during treatment; 127 patients (78%) completed the planned chemoradiation regimen without any treatment modification.

Table 2. Treatment Modifications in Patients With Esophageal Cancer During Curative Neoadjuvant Chemoradiation (N = 162).

Characteristic	Total No.	No. (%)
Any treatment modification	160	35 (22)
Delay CR	162	13 (8)
Dose reduction CT	160	15 (9)
Dose reduction RT	162	2 (1)
Hospitalization	161	18 (11)
Discontinuation CR	162	3 (2)
Mortality	162	0

CR, curative neoadjuvant chemoradiation; CT, chemotherapy; RT, radiotherapy.

Parameters of Nutrition Status and Treatment Modifications

Table 3 shows the results of the univariate logistic regression analyses between each parameter of nutrition status and treatment modifications during neoadjuvant chemoradiation. The only statistically significant association was observed for HGS.

Discussion

This study describes the association between pretreatment nutrition status of patients with esophageal cancer and treatment modifications during chemoradiation in a group of patients that was intensively nutritionally supervised during treatment. The results show that only pretreatment HGS was statistically significantly associated with treatment modifications.

Nutrition Status and Treatment Modifications

In contrast to older studies that showed a high prevalence of malnutrition (60%–85%) in patients with esophageal cancer,^{8,10,24} our patients presented with a relatively good baseline nutrition status. According to the new ESPEN definition for malnutrition, 12% of our study population was defined as malnourished at diagnosis.²⁰ Whereas in the previous century, alcohol and smoking²⁵ were identified as known risk factors for esophageal cancer, nowadays overweight and obesity are well-known risk factors.^{26–28} This may explain the relatively low percentage of malnutrition. Indeed, in our study population, the mean BMI at diagnosis was 25.1 kg/m², which is comparable to other recent studies in patients with esophageal cancer.^{2,27,29} Despite the high BMI, many patients presented with concurrent unintentional weight loss, likely due to cancer cachexia or wasting as a result of obstruction of the esophagus by the tumor.²⁶ In our study population, 46% of the patients were overweight, while at the same time 33% had a mean pretreatment weight loss of >5% body weight in the 6 months prior to diagnosis.

Furthermore, it has been suggested that patients with cancer may have a lower FFM than healthy controls.^{26,30} FFM is

important in these patients, since FFM is crucial in the distribution of chemotherapy throughout the body.^{31,32} In our study population, 36% of the patients had a FFMI below the 10th percentile of normative values. Currently, a chemotherapy dose is based on body surface,³⁰ and recent studies have shown that this may lead to an overdose of chemotherapy and increased treatment toxicity in patients with a low FFMI or sarcopenia.^{26,31,32} In our study, we did not find an association between FFM or FFMI and treatment modifications during neoadjuvant chemoradiation. This might be due to lack of power, as previous studies included a larger number of patients.^{31,32} Furthermore, it has been suggested that muscle quality, determined by computed tomography scan, may be more important in relation to treatment toxicity than FFM.^{33,34} Muscle quality was not measured in our study or in the above-mentioned studies.^{31,32} Further research to examine the role of low muscle mass and muscle quality among patients with esophageal cancer in relation to treatment modifications during neoadjuvant chemoradiation is recommended.

HGS and Treatment Modifications

Our study is in line with previous studies in other patient groups that suggest an association between a lower pretreatment HGS and an increased risk for adverse events during treatment.^{35–38} However, the demonstrated association in this study was marginal ($P = .05$). Our patients presented with a relatively high mean HGS of 35.5 kg, compared with 24.3–27.8 kg in previous studies,^{36,39} which is in line with the relatively good nutrition status at baseline. After dichotomizing (HGS <, >= the 10th percentile of normative values), the association with treatment modifications no longer existed. Therefore, and based on the results of the present study, it is difficult to advise cutoff points for HGS that may indicate the need for extra (nutrition and exercise) support.

As mentioned before, our patients presented with a relatively good baseline nutrition status. However, maintaining a good nutrition status during treatment is another challenge. Another study has shown a decline of muscle mass and strength at all disease stages in patients with esophageal cancer.²⁶ This raises the question of whether physical training in addition to nutrition intervention before chemoradiation could be effective to maintain HGS or FFM in patients with esophageal cancer. Unfortunately, our study had no data on physical training. It has been demonstrated that strength training in patients with esophageal cancer is effective in reducing muscle loss and maintaining muscle strength.⁴⁰ In addition, it has been shown that a combination of resistance and aerobic exercise training during chemotherapy in women with breast cancer improved muscle strength and reduced dose reductions.⁴¹ Further research to examine whether physical training could be effective to maintain muscle mass and muscle strength and to prevent treatment modifications during neoadjuvant chemoradiation in patients with esophageal cancer is recommended.

Table 3. Association Between Pretreatment Parameters of Nutrition Status in Patients With Esophageal Cancer and Treatment Modifications During Neoadjuvant Chemoradiation.

Characteristic	Model 1 ^a			Model 2 ^b		
	OR	95% CI	P Value	OR	95% CI	P Value
HGS, kg	0.938	0.883–0.996	.037	0.939	0.882–1.000	.050
FFMI, kg	1.130	0.928–1.378	.224	1.111	0.897–1.376	.337
Weight loss last 6 months, kg	0.990	0.903–1.086	.838	0.996	0.906–1.094	.996
BMI, kg/m ²	0.995	0.915–1.083	.912	0.986	0.906–1.074	.754
FMI, kg	1.010	0.917–1.051	.612	1.003	0.961–1.047	.883
Energy intake vs requirement, %	0.998	0.979–1.018	.860	1.001	0.982–1.020	.926
Protein intake vs requirement, %	0.995	0.976–1.016	.657	0.998	0.979–1.019	.874

Bold formatting indicates statistically significant values. BMI, body mass index; FMI, fat mass index; FFMI, fat-free mass index; HGS, handgrip strength; OR, odds ratio.

^aAdjusted for age and sex.

^bAlso adjusted for previous tumor and American Society of Anesthesiologists and tumor node classification.

Intensive Dietary Care Program

It has been shown that nutrition intervention decreases preoperative weight loss and postoperative complications in patients with esophageal cancer.² Therefore, our patients currently receive intensive nutrition counseling throughout the complete neoadjuvant chemoradiation treatment trajectory, starting at diagnosis. This may be one of the reasons why we found only few associations between parameters of nutrition status and adverse events during chemoradiation.

Strengths and Limitations

Strengths of this study include the homogeneous group of patients with esophageal cancer and the intensive nutrition support as part of a standard clinical care trajectory. However, as with observational studies, results should be interpreted with caution and no causal links can be drawn. Furthermore, data for this study were obtained from routine clinical practice and not specifically collected for research purposes. Nevertheless, measurements were performed in most patients as part of the standard dietetic care.

Conclusion

In conclusion, out of a variety of nutrition parameters, only a lower pretreatment HGS was associated with treatment modifications during neoadjuvant chemoradiation. FFMI, BMI, and protein and energy intake were not associated with treatment modifications. Our patients presented with a relatively good baseline nutrition status. In addition, patients received intensive nutrition counseling during treatment. This may possibly explain why nutrition status may have been of little influence on the occurrence of treatment modifications in this specific patient group. Further research is recommended to examine whether HGS is a clinically relevant measurement tool to identify patients with esophageal cancer at risk for treatment modifications during neoadjuvant chemoradiation and whether

resistance training leads to improved HGS and consequently to less treatment modifications.

Statement of Authorship

P. Lakenman and M. de van der Schueren contributed to the conception/design and the acquisition, analysis, and interpretation of the data; P. Lakenman, J. Witvliet-van Nierop, and K. Ottens-Oussoren drafted the manuscript; P. Lakenman, D. van der Peet, and M. de van der Schueren critically revised the manuscript; and P. Lakenman, J. Witvliet-van Nierop, K. Ottens-Oussoren, and D. van der Peet agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

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