



# Impact of body composition and physical strength changes during chemoradiotherapy on complications and survival after oesophagectomy

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## ABSTRACT

**Background:** The aim of this study was to assess body composition and physical strength changes during neoadjuvant chemoradiotherapy (nCRT) and assess their predictive value for (severe) postoperative complications and overall survival in patients who underwent oesophagectomy for oesophageal cancer.

**Methods:** Consecutive patients who underwent nCRT and oesophagectomy with curative intent in a tertiary referral center were included in the study. Perioperative data were collected in a prospectively maintained database. The CT images before and after nCRT were used to assess skeletal muscle index (SMI), subcutaneous fat index (SFI), and visceral fat index (VFI). To assess physical strength, handgrip strength (HGS) and the exercise capacity of the steep ramp test (SRT Wpeak) were acquired before and after nCRT.

**Results:** Between 2015 and 2020, 126 patients were included. SMI increased in female subgroups and decreased in male subgroups (35.38 to 35.60 cm<sup>2</sup>/m<sup>2</sup> for females, P value 0.048, 46.89 to 45.34 cm<sup>2</sup>/m<sup>2</sup> for males, P value < 0.001). No significant changes in SFI, VFI, HGS, and SRT Wpeak were observed. No predictive value of changes in SMI, HGS, and SRT Wpeak was shown for (severe) postoperative complications and overall survival.

**Conclusions:** A significant but minimal decrease in SMI during nCRT was observed for males only, it was not associated with postoperative complications or overall survival. Physical strength measurements did not decrease significantly over the course of nCRT. No associations with postoperative complications or overall survival were observed.

## 1. Introduction

In mainland Europe, the curative treatment for oesophageal cancer consists of neoadjuvant chemoradiotherapy (nCRT) followed by an oesophagectomy [1]. Oesophageal cancer leads to changes in body composition and a reduction of physical strength due to multiple mechanisms, such as malnutrition, inactivity and tumor-related cytokines [2]. Also, neoadjuvant treatment and surgery have a significant impact on the patients' body composition and physical fitness [3,4]. Changes in body composition such as a decrease in muscle mass and physical strength are associated with a reduced prognosis [5,6]. A standardized indicator of body composition and physical fitness of cancer patients is sarcopenia. Sarcopenia is the progressive and generalized loss of muscle function and mass [7]. Numerous methods have been proposed to assess muscle mass. CT scans are suitable to quantify muscle mass and widely available since they are performed routinely in cancer patients. To assess muscle function, the other parameter of

sarcopenia, multiple clinical tests are available. Commonly performed physical tests include handgrip strength, leg extension strength, Timed Up and Go (TUG) and the steep ramp test [8,9].

Recent systematic reviews demonstrated that preoperative low muscle mass is a predictive factor for both postoperative complications and mortality in various oncological subtypes [6,10]. Additionally, a reduced preoperative physical performance was associated with severe complications [11,12]. Visceral and subcutaneous fat composition showed predictive value for outcomes of oesophageal cancer patients in a similar manner across studies [13,14]. Moreover, studies in other cancer subtypes demonstrated that a decrease in skeletal muscle mass during neoadjuvant therapy is a predicting factor for adverse clinical outcomes [15,16]. However, results in oesophageal cancer remain inconclusive, both regarding the change of body composition as well as the reduction of physical strength during neoadjuvant therapy [17,18]. In addition to its use in prognostication, loss of skeletal muscle and physical strength are potentially modifiable and may be targeted with

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prehabilitation strategies.

The aim of this retrospective cohort study was to assess body composition changes and changes in physical strength measurements before and after neoadjuvant chemoradiotherapy for oesophageal cancer. Secondly, the predictive value of skeletal muscle mass changes and absolute values and changes in physical strength measurements and absolute values for postoperative complications and overall survival was assessed.

## 2. Methods

### 2.1. Study design

In this retrospective cohort study, data was collected from a prospectively maintained surgical database from the University Medical Center Utrecht (UMCU). In accordance with the Institutional Review Board informed consent requirement was waived for this study.

### 2.2. Study population

All consecutive patients with oesophageal or gastro-oesophageal junction cancer who underwent nCRT followed by an oesophagectomy between September 2015 and January 2020 in the UMCU were eligible for inclusion. Patients with missing CT scans before or after nCRT were excluded. nCRT consisted of weekly intravenous administration of carboplatin (area under the curve two) and paclitaxel (50 mg/m<sup>2</sup>) for five weeks with concurrent radiotherapy (41.4 Gy in 23 fractions of 1.8 Gy).

### 2.3. Dietary and physiotherapeutic prehabilitation strategy

Before and 2 weeks after nCRT nutritional assessment followed by dietary counselling is provided by a registered dietitian. An individualized nutrition care plan is given to all patients to meet the energy and protein requirements, conforming with the guidelines for surgical patients as recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) [19]. Additional consultations are provided for patients experiencing (risk for) malnutrition during the preoperative phase [20]. Patients are advised to walk for 30 min daily to promote physical activity and reduce sedentary behaviour. No other physiotherapy interventions are typically provided during nCRT.

### 2.4. Assessment of body composition

In this study, the following indicators were used to assess body composition: skeletal muscle index (SMI), low muscle mass, visceral fat index (VFI), and subcutaneous fat index (SFI). Changes in body composition indicators were measured using the CT scans before and after nCRT. Contrast as well as non-contrast enhanced scans were included, obtained using Philips scanners. The CT acquisition parameters were 120 kVp and slice thickness of 5 mm.

A cross sectional slice at the height of the third lumbar vertebra was used and analyzed by CoreSlicer, a validated web-based tool to assess body composition semi-automatically [21]. The CoreSlicer tool uses Hounsfield unit ranges of −190 to −30 for fat tissue and −29 to 150 for skeletal muscle. Body composition assessment was performed by a single blinded investigator with experience with CoreSlicer. A quality check of the body composition assessment was performed by an experienced radiologist (WV), who was blinded for the study outcomes.

The skeletal muscle area was divided by the height squared to calculate the skeletal muscle index (SMI) (cm<sup>2</sup>/m<sup>2</sup>). Similarly, visceral (VFI) and subcutaneous fat indices (SFI) were calculated. Body composition parameters before and after nCRT are provided for male and female patients separately. Changes in SMI during nCRT were calculated. The SMI limit for low muscle mass was less than 52.4 cm<sup>2</sup>/m<sup>2</sup> for men and less than 38.5 cm<sup>2</sup>/m<sup>2</sup> for women, according to cut-off values published by Prado et al. [22] These cut-off values are commonly used in

previous literature [23–25].

### 2.5. Physical strength measurements

Physical strength measurements included handgrip strength and the steep ramp test. Both tests were performed routinely as part clinical care and conducted by certified physiotherapists. Handgrip strength (in kg) was evaluated using the Jamar handheld dynamometer (Lafayette Instrument Company, USA) and a 6.5 kg change is assumed to be of clinical relevant difference [26]. The steep ramp test is a short maximal cycle ergometer test. Patients are requested to cycle at a pedal frequency of 70–80 rpm while the workload is increased by 25 Watt every 10 s [4]. Exercise capacity (Wpeak) was reported as the main outcome parameter of the steep ramp test [27].

### 2.6. Primary outcomes

The primary outcomes of this study are total postoperative complications, severe postoperative complications, and overall survival. Complications were graded according to the Clavien-Dindo classification system, severe postoperative complications were defined as complications with a Clavien-Dindo grade equal to or greater than IIIa [28]. Survival data was obtained from the electronic patient files.

### 2.7. Statistical analysis

Patient and tumor characteristics were described as counts with percentages, means with standard deviations, or medians with ranges where appropriate. The missing data pattern regarding physical strength measurements was analyzed and considered to be missing at random. As such, missing data was imputed using the Multivariate Imputation by Chained Equations (MICE) package in R software with fifty iterations and twenty imputed datasets [29]. The quantity of missing data per variable before imputation is presented in Table 2.

To test for significant body composition changes during nCRT (paired patient groups) the Wilcoxon test was used for non-normally distributed data and McNemar's test for binomial data. To test for significant differences in postoperative complications between two non-paired groups a chi-square test was used for binomial data. A Fisher's exact test was performed instead of a chi square test if two or more cell sizes included fewer than 5 events. The correlation between muscle mass and physical test measurements was calculated using the Spearman's rank correlation coefficient.

Multivariable binary logistic regression was used for the analyses of (severe) postoperative complications and a cox regression analysis for survival analysis. Variables with clinical relevance were selected in advance for inclusion in the multivariable logistic and cox regression analyses. To ensure the analysis focused on predictive value in a pre-operative setting, our regression models were constructed using only preoperative variables. A P value lower than 0.05 was deemed statistical significant and all statistical analyses were performed in SPSS version 25.0 (IBM, Armonk, New York, USA) and R software for statistical computing version April 1, 1717 ([www.R-project.org](http://www.R-project.org)).

## 3. Results

In total, 126 patients were eligible for inclusion. 78% were male and the tumor histology was predominantly adenocarcinoma (71%, vs. 29% squamous cell carcinoma). 90% of the patients had cancer T-stage 3 and 73% had locoregional lymph node metastases. The majority of patients had a tumor located in the distal oesophagus (75%). The complete patient cohort underwent nCRT according to the CROSS regimen [30]. 3 patients (2%) discontinued nCRT due to the following adverse events: oesophagitis, leukopenia, and thrombocytopenia. 99% of the patients underwent a (robot-assisted) laparoscopic/thoracoscopic oesophagectomy, One patient (1%) underwent an open oesophagectomy in

combination with a laryngectomy. The median interval between the pre-nCRT and post-nCRT CT scan was 14 weeks (IQR 3) and median interval between the physical strength measurements was 8 weeks (IQR 3). A complete overview of patient and tumor characteristic has been provided in [Table 1](#).

### 3.1. Body composition changes during neoadjuvant chemoradiotherapy and anthropometry for females

For females, the median body mass index (BMI) prior to nCRT was 23.87 kg/m<sup>2</sup>, which decreased to 22.90 kg/m<sup>2</sup> after nCRT (P value 0.011). Low muscle mass rates did not alter significantly during nCRT (71%–68%, P value 1.000). SMI increased significantly over the course of nCRT from 35.38 to 35.60 cm<sup>2</sup>/m<sup>2</sup> (P value 0.048). SFI and VFI did not show any significant changes during nCRT.

### 3.2. Body composition changes during neoadjuvant chemoradiotherapy and anthropometry for males

The median body mass index (BMI) prior to nCRT was 25.74 kg/m<sup>2</sup> for male patients ([Table 2](#)). After nCRT, median BMI was 25.26 kg/m<sup>2</sup> (P value 0.060). A significant increase of low muscle mass rates was observed from 77% before nCRT to 87% after nCRT (P value 0.003). SMI decreased significantly over the course of nCRT (46.89–45.34 cm<sup>2</sup>/m<sup>2</sup>, P value 0.000). SFI and VFI did not show any significant changes during nCRT.

### 3.3. Physical strength changes during neoadjuvant chemoradiotherapy for females

For women, the median HGS was 28.23 kg before nCRT and 27.23 kg after nCRT (P value 0.534). The median Wpeak as measured with the SRT increased from 186.50 before nCRT to 173.02 W after nCRT in the female patients (P value 0.158).

### 3.4. Physical strength changes during neoadjuvant chemoradiotherapy for males

For men, the median HGS decreased from 41.06 to 40.24 kg during nCRT (P value 0.066). The median Wpeak as measured with the SRT showed a decrease from 243.53–221.47 W (P value 0.085). Absolute and percentage changes of body composition and physical strength measurements are presented in [Table S1](#).

### 3.5. Correlation between skeletal muscle index and physical tests

A Spearman's rank correlation coefficient was performed to investigate the correlation between SMI and physical strength tests ([Table S2](#)). Between SMI and HGS, a correlation coefficient of 0.32 and 0.49 was found pre nCRT and preoperatively, respectively. Between SMI and Wpeak during the SRT, a correlation coefficient of 0.20 and 0.34 was found pre nCRT and preoperatively, respectively. This indicates weak to moderate correlation between SMI and physical strength measurements.

### 3.6. Multivariable analysis of skeletal muscle loss and changes in physical strength measurements and total postoperative complications

79% of the patients had a postoperative complication (Clavien-Dindo I–V, 35% pneumonia, 31% anastomotic leakage, 16% jejunostomy-related complications). A binary logistic regression analysis was performed to assess the predictive value of skeletal muscle loss and changes in physical strength measurements for total postoperative complications (Clavien-Dindo I–V), accounting for clinically relevant variables.

None of the included parameters demonstrated an association with total postoperative complications ([Table 3](#)). SMI decrease in percentages

**Table 1**

Overview of patient characteristics.

	Total (n = 126)
Age (years), mean (SD)	66.12 (8.12)
Sex	
Male	98 (78%)
Female	28 (22%)
ASA grade	
I	7 (6%)
II	77 (61%)
III	39 (31%)
Missing	3 (2%)
Co-morbidity	
None	28 (22%)
Cardiac	27 (21%)
Diabetes	25 (20%)
Pulmonal disease	33 (26%)
Vascular	55 (44%)
Cell type	
Adenocarcinoma	89 (71%)
Squamous cell carcinoma	37 (29%)
cT category	
T2	10 (8%)
T3	113 (90%)
T4a	3 (2%)
cN category	
N0	34 (27%)
N+	91 (72%)
Missing	1 (1%)
cM category	
M0	126 (100%)
Tumor location	
Upper oesophagus	5 (4%)
Middle oesophagus	15 (12%)
Lower oesophagus	95 (75%)
Gastroesophageal junction/Cardia	7 (6%)
Missing	3 (2%)
Neoadjuvant treatment	
Chemoradiotherapy	126 (100%)
Completion of neoadjuvant chemoradiotherapy	123 (98%)
Mandard score	
I	40 (32%)
II	18 (14%)
≥III	61 (49%)
Missing	7 (6%)
Procedure type	
Transhiatal oesophagectomy	31 (25%)
Trans thoracic oesophagectomy	95 (75%)
Approach	
Open operation	1 (1%)
(Robot-assisted) Laparoscopic /thorascopic	125 (99%)
Pre nCRT CT scan available	126 (100%)
Post nCRT CT scan available	126 (100%)
Pre nCRT handgrip strength available	77 (61%)
Missing	49 (39%)
Post nCRT handgrip strength available	83 (66%)
Missing	43 (34%)
Pre nCRT steep ramp test	55 (44%)
Missing	71 (56%)
Post nCRT steep ramp test	73 (58%)
Missing	53 (42%)
Intervals (weeks), median (IQR)	
CT before start of nCRT	3 (2)
CT before surgery	4 (4)
Time between CT scans	14 (3)
Physical test before start of nCRT	0 (1)
Physical test before surgery	7 (4)
Time between physical tests	8 (3)
Time interval between end of nCRT and surgery	11 (4)
Outcomes	
Total complications	99 (79%)
Severe complications	49 (39%)
3-year overall survival	37%

ASA: American Society of Anesthesiologists; IQR: interquartile range; nCRT: neoadjuvant chemoradiotherapy; SD: standard deviation.

**Table 2**

Body composition and physical strength changes during nCRT and anthropometry in female (n = 28) and male (n = 98) patients.

Variable	Pre nCRT (female)	Pre surgery (female)	P value	Pre nCRT (male)	Pre surgery (male)	P value	Missings
Height in m (median, IQR)	1.66 (0.09)			1.80 (0.10)			0%
Weight in kg (median, IQR)	65.50 (16.00)	64.00 (16.40)	0.015	81.50 (17.00)	80.00 (14.10)	0.066	0%
BMI in kg/m <sup>2</sup> (median, IQR)	23.87 (4.27)	22.90 (3.62)	0.011	25.74 (4.53)	25.26 (3.68)	0.060	0%
SMI in cm <sup>2</sup> /m <sup>2</sup> (median, IQR)	35.38 (6.85)	35.60 (9.69)	0.048	46.89 (9.18)	45.34 (8.23)	<0.001	0%
Low muscle mass <sup>a</sup> (n, %)	20 (71)	19 (68)	1.000	75 (77)	85 (87)	0.003	0%
SFI in cm <sup>2</sup> /m <sup>2</sup> (median, IQR)	66.69 (45.07)	65.59 (43.04)	0.080	44.18 (31.25)	46.09 (27.83)	0.786	0%
VFI in cm <sup>2</sup> (median, IQR)	51.06 (53.41)	48.70 (34.22)	0.258	66.86 (45.26)	69.92 (36.89)	0.269	0%
HGS in kg (median, IQR)	28.23 (3.85)	27.23 (3.85)	0.534	41.06 (16.66)	40.24 (15.74)	0.066	37%
Wpeak of SRT in W (median, IQR)	186.50 (66.16)	173.02 (73.84)	0.158	243.53 (91.85)	221.47 (117.28)	0.085	49%

HGS: handgrip strength; IQR: Interquartile range; SMA: skeletal muscle area; SMI: skeletal muscle index; SFA: subcutaneous fat area; SFI: subcutaneous fat index; VFI: visceral fat index; W: Watt.

<sup>a</sup> According to cut-off values published by Prado et al. [22].

**Table 3**

Binary logistic regression analysis of loss of skeletal muscle and physical strength parameters and total postoperative complications.

Variable	OR	CI 95%	P value
Male gender	0.29	0.06–1.33	0.114
BMI	1.05	0.93–1.19	0.426
Age	1.02	0.96–1.07	0.570
Clinical T stage			
T2			Ref.
T3	0.62	0.08–4.93	0.654
T4a	0.41	0.02–10.70	0.590
ASA score			
<III			Ref.
III	2.99	0.80–11.21	0.107
Surgical procedure			
Transthoracic vs. transhiatal oesophagectomy	2.51	0.83–7.60	0.107
Comorbidity	2.48	0.89–6.94	0.086
% SMI decrease	1.00	0.94–1.06	0.946
% HGS decrease	1.03	0.98–1.08	0.198
% SRT Wpeak decrease	0.99	0.96–1.03	0.198

ASA: American Society of Anesthesiology; BMI: body mass index; CI: confidence interval; HGS: handgrip strength; OR: odds ratio; SMI: skeletal muscle index; SRT: steep ramp test; Ref.: reference category; W: Watt.

did not significantly increase the odds of total postoperative complications (OR 1.00; CI 95% 0.94–1.06; P value 0.946). Likewise, HGS decrease in percentages showed an OR of 1.03 (CI 95% 0.98–1.08; P value 0.198) and SRT Wpeak decrease in percentages showed an OR of 0.99 (95% CI 0.96–1.03; P value 0.198) for total postoperative complications.

### 3.7. Multivariable analysis of skeletal muscle loss and changes in physical strength measurements and severe postoperative complications

Binary logistic regression analysis demonstrated that decrease in SMI in percentages was not associated with a higher risk of severe postoperative complications (OR 0.96; CI 95% 0.91–1.00; P value 0.073). Accordingly, decrease of HGS and SRT Wpeak in percentages did not demonstrate to be of predictive value for severe complications (Table 4).

### 3.8. Analysis of skeletal muscle loss and changes in physical strength measurements and overall survival

Three-year overall survival was 37% with a median follow-up of 24 months. Cox regression analysis demonstrated that SMI decrease in percentages is not associated with overall survival (HR 1.01; 95% CI 0.99–1.03; P value 0.436). Similarly, decrease in HGS and SRT Wpeak VFI did not show significant predictive value for overall survival (% HGS decrease: HR 0.98; 95% CI 0.96–1.00; P value 0.129; % SRT Wpeak decrease: HR 0.99; CI 95% 0.98–1.0; P value 0.558). cT4a and ASA III was associated with worse overall survival. The complete overview of the cox regression analysis is provided in Table 5.

**Table 4**

Logistic regression analysis of loss of skeletal muscle and physical strength parameters and severe postoperative complications.

Variable	OR	CI 95%	P value
Clinical T stage			
T2			Ref.
T3	0.90	0.06–1.47	0.138
T4a	1.32	0.08–22.31	0.848
ASA score			
<III			Ref.
III	1.80	0.79–4.10	0.163
% SMI decrease	0.96	0.91–1.00	0.073
% HGS decrease	1.00	0.97–1.03	0.974
% SRT Wpeak decrease	0.99	0.96–1.02	0.440

ASA: American Society of Anesthesiology; BMI: body mass index; CI: confidence interval; HGS: handgrip strength; OR: odds ratio; SMI: skeletal muscle index; SRT: steep ramp test; Ref.: reference category; W: Watt.

**Table 5**

Cox regression analysis of loss of skeletal muscle and physical strength parameters and overall survival.

Variable	HR	CI 95%	P value
Male gender	0.88	0.48–1.61	0.673
Age	1.02	0.99–1.05	0.137
Clinical T stage			
T2			Ref.
T3	2.17	0.70–6.74	0.187
T4a	12.64	2.50–64.02	0.003
Histology			
Adenocarcinoma			Ref.
Squamous cell carcinoma	1.15	0.65–2.03	0.627
ASA score			
<III			Ref.
III	1.76	1.02–3.03	0.048
% SMI decrease	1.01	0.99–1.03	0.436
% HGS decrease	0.98	0.96–1.00	0.129
% SRT Wpeak decrease	0.99	0.98–1.01	0.558

ASA: American Society of Anesthesiology; BMI: body mass index; CI: confidence interval; HGS: handgrip strength; OR: odds ratio; SMI: skeletal muscle index; SRT: steep ramp test; Ref.: reference category; W: Watt.

### 3.9. Multivariable analysis of absolute values of skeletal muscle index and physical strength measurements and (severe) complications and overall survival

In the supplementary material binary logistic regression analysis is presented using absolute values of SMI, HGS and Wpeak of the SRT, measured preoperatively (Tables S3–5). No predictive value for (severe) complications or survival was observed.



#### 4. Discussion

This study evaluated changes in body composition and physical strength measurements during nCRT in a cohort of oesophageal cancer patients, treated with curative intent. The predictive value of changes in skeletal muscle mass and physical strength measurements for postoperative complications and overall survival was investigated. The changes observed were limited and not clinically relevant. This cohort of oesophageal cancer patients showed a significant decrease of SMI during nCRT in the male subgroup. Subcutaneous and visceral fat did not change significantly during nCRT for both genders. Physical strength measurements, including HGS and the SRT, decreased over the course of nCRT, but without statistical significance. No association was observed between change and absolute values of SMI, HGS, or SRT, and (severe) postoperative complications and overall survival.

Malnutrition, cachexia, and low muscle mass are common in oesophageal cancer patients. A recent meta-analysis reported a low muscle mass rate of 52% for oesophageal cancer patients and 35% in general cancer populations [31]. Prevalence of low muscle mass in the general population of the sixth and seventh decade is 5–13% [32–34]. In the current patient cohort, low muscle mass rates after nCRT were even higher compared to other study populations of oesophageal cancer patients (87% for men, 68% for women in our study) [35].

In this study, the limited changes in body composition and physical strength measurements during nCRT can be explained by the already poor muscle status at baseline. Most likely, dietetic and physiotherapy interventions as part of our local prehabilitation program have prevented further deterioration of the included patients in terms of muscle mass and function. These may be reasons why muscle mass and physical strength changes during nCRT did not show predictive value for (severe) postoperative complications and overall survival.

Other studies have previously published similar decreases in SMI over the course of neoadjuvant therapy [36,37]. Most studies report a negative prognostic value of skeletal muscle mass loss for overall survival and demonstrate no effect on postoperative complications [37,38]. Previously published studies also describe reductions in physical tests scores after neoadjuvant chemotherapy [39,40]. Studies reporting on the effect of changes in physical strength on outcomes in oesophageal cancer are rare. A previous Western study reported that impaired physical fitness as assessed using the 30 s stand test before nCRT was associated with overall survival [41]. No associations were observed between physical strength tests before and after nCRT and postoperative complications. This previous study did not report on the effect of changes in physical strength measurements and its predictive value for postoperative complications and overall survival.

Muscle mass loss and loss of muscle function is caused by multiple factors, e.g. sedentary lifestyle, age, feeding issues, or tumor related cytokines. Different mechanisms that induce muscle mass loss might influence specific outcomes, such as overall survival or postoperative complications. This might give an explanation for the inconsistent conclusions of studies investigating the predictive value of loss in muscle mass. Similarly, changes in physical strength measurements are also multifactorial. In literature, it is commonly stated that completion of nCRT can be interpreted as a test of physical fitness and general condition of a patient [39,42]. This might explain the impaired overall survival of patients with more muscle mass loss during nCRT, as demonstrated in some previous studies [37,38]. Still, the observed reduction in muscle mass during nCRT in this study may be a direct effect of nCRT, or may be a consequence of alternative factors including sedentary lifestyle, age, feeding issues, or tumor related cytokines.

Our study findings support the notion that changes in muscle mass and function during nCRT may have limited clinical value in predicting postoperative complications and overall survival. This is particularly evident within a cohort with pre-existing low muscle mass and participating in a prehabilitation program. Nevertheless, it remains widely accepted that frailty or sarcopenia screening and prehabilitation before

surgery holds significant clinical importance [2,43,44].

This study has a number of limitations to consider. Firstly, a significant proportion of the included patients had missing values regarding the physical strength measurements. The missing values were replaced using multiple imputation, an advanced method to handle missing data which takes the uncertainty in predicting missing values into account by creating multiple complete datasets [29]. Inclusion of physical test data is crucial in sarcopenia research as it, along with muscle mass assessment, is a fundamental component of the condition [7]. Lastly, due to the retrospective character of this study, timing of physical tests and CT-scans were dictated by clinical care. This resulted in different time intervals between the CT scans compared with the physical tests measurements. Also the optimal time intervals for muscle mass and strength measurements could not be assessed, which may have influenced their predictive value for complications and survival. Strengths of this study are the relatively large sample size, use of pre and post treatment scans which enabled accurate assessment of changes in body composition, and the combination of muscle mass and physical strength changes during nCRT for prediction of complications and overall survival.

Future research should be prospective in nature to identify optimal time intervals for physical test measurements. Preferably, data regarding physiotherapy and dietetic interventions are recorded. Also, a standardized method to assess physical strength is warranted to increase comparability of future studies, such as handgrip strength. In this way the precise effect of changes in muscle mass and physical strength on short- and long term clinical outcomes can be assessed.

In conclusion, in this cohort of oesophageal cancer patients treated with curative intent, a limited decrease in SMI during nCRT was observed for males only, but it was not associated with postoperative complications or overall survival. Physical strength measurements did not decrease significantly over the course of nCRT. No associations of changes and absolute values of physical strength measurements with (severe) postoperative complications or overall survival were observed.

#### CRedit authorship contribution statement

**R.B. den Boer:** Conceptualization, Formal analysis, Methodology, Writing – original draft. **I.L. Defize:** Data curation, Writing – original draft, Methodology. **W. Veldhuis:** Supervision, Formal analysis, Writing – review & editing. **E. Steenhagen:** Data curation, Writing – review & editing. **A. Kerst:** Conceptualization, Writing – review & editing. **R. van Hillegersberg:** Conceptualization, Methodology, Writing – review & editing. **P.A. de Jong:** Conceptualization, Supervision, Writing – review & editing. **J.P. Ruurda:** Conceptualization, Supervision, Writing – review & editing.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejso.2023.107017>.

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