Associations of Pretreatment Physical Status Parameters with Tolerance of Concurrent Chemoradiation and Survival in Patients with Non-small Cell Lung Cancer

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Associations of Pretreatment Physical Status Parameters with Tolerance of Concurrent Chemoradiation and Survival in Patients with Non-small Cell Lung Cancer

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Abstract

Objective The aim of this study was to evaluate associations between pretreatment physical status parameters and tolerance of concurrent chemoradiation (cCHRT) and survival among patients with stage III non-small cell lung cancer (NSCLC).

Methods A retrospective cohort study was conducted among patients with stage III NSCLC who had received cCHRT between 2006 and 2015. Multivariate independent associations were analysed between the pretreatment parameters age, Charlson comorbidity index, World Health Organization performance status (WHO performance status), body mass index (BMI), fat-free mass index (FFMI), maximal handgrip strength, forced expiratory volume in one second and carbon monoxide lung diffusion capacity on the one hand with tolerance of cCHRT (defined as a received radiation dose at least equal to the prescribed radiation dose) and survival on the other hand.

Results 527 of 577 patients (91.3%) tolerated cCHRT. A WHO performance status ≥ 2 (odds ratio (OR) 0.43) and BMI < 18.5 kg/m^2 (OR 0.36) were associated with poorer tolerance of cCHRT. In the total group, a WHO performance status ≥ 2 (hazard ratio (HR) 1.73), low FFMI (HR 1.23) and intolerance of cCHRT (HR 1.55) were associated with poorer survival.

Conclusion In patients with stage III NSCLC receiving cCHRT, poor WHO performance status and BMI < 18.5 kg/m^2 were independently associated with tolerance of cCHRT. Physical status parameters and intolerance of cCHRT were independently associated with poorer survival. Besides using this information for treatment decisions, optimizing physical status in patients at risk for intolerance of cCHRT might be a next step for improving treatment outcomes.

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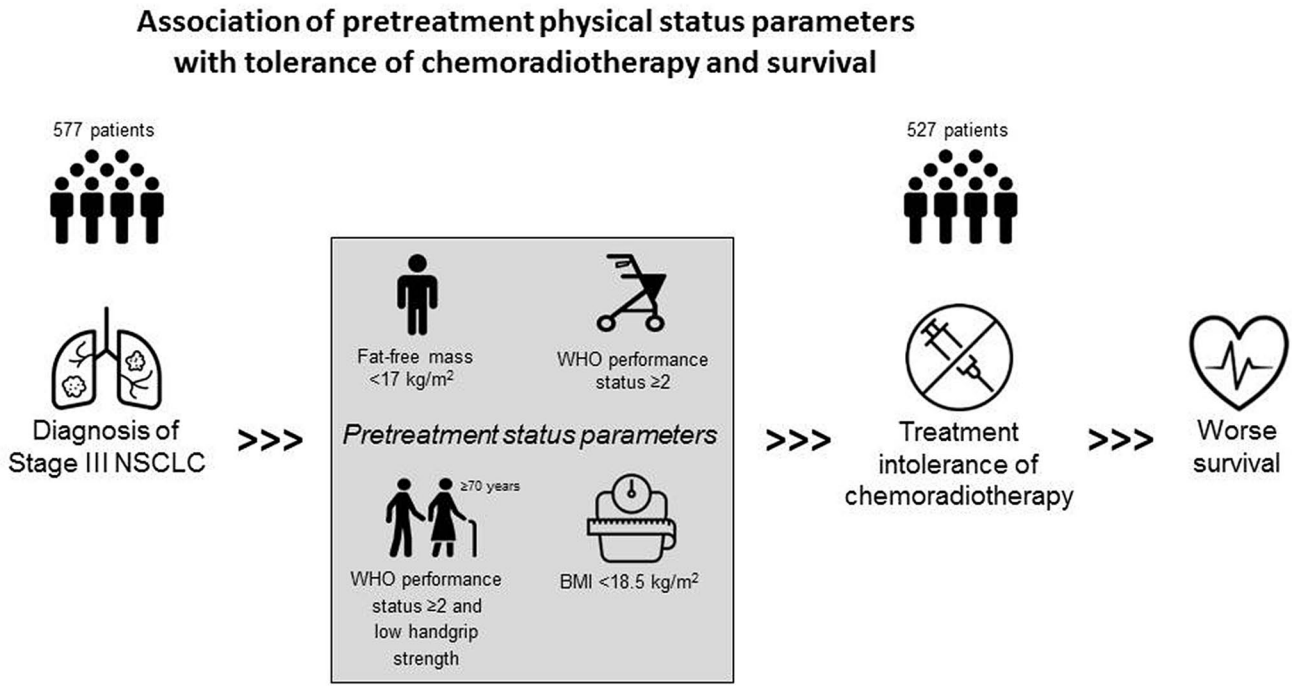
Graphic Abstract



Keywords Non-small cell lung cancer · Concurrent chemoradiation · Treatment tolerance · Survival · Pretreatment risk assessment

Introduction

Lung cancer is the fourth most common type of cancer in the Netherlands [1], with 14,500 newly diagnosed patients in 2017 [2]. Non-small cell lung cancer (NSCLC) accounts for 75% of all lung cancers [2]. About one-fourth present with stage III which has a poor five-year survival rate [3]. The preferred treatment for relatively fit patients with stage III NSCLC is concurrent chemoradiation (cCHRT) [4]; however, this treatment option is very intensive and often accompanied by serious complications, including hospitalization and mortality [5].

The majority of patients are older (≥ 70 years). Patients at high risk for intolerance of CHRT are characterized as aged ≥ 70 years and those suffering from anorexia, dysphagia, fatigue and physical inactivity [9–11]. Although a geriatric assessment might identify older patients who are at risk for treatment complications [12], it is still unclear to what extent these tests individually, or in combination, are associated with treatment tolerance in patients with NSCLC [13–16]. Evidence regarding treatment options and outcomes are scarce for older patients with NSCLC and evidence-based insights are highly needed for this vulnerable population. Older patients are under-represented in clinical trials, and those older patients who are included are generally selected fit patients without comorbidity. This means that the external validity of clinical trial results for the real-world population of older patients with cancer is low [6], especially since polypharmacy, frailty, poor performance status, long-term physical inactivity and smoking-related comorbidities characterize patients with stage III NSCLC [5, 7, 8].

It is, therefore, important to gain real-world insight into modifiable parameters that might be prognostic for tolerance of cCHRT and survival and identify patients at high risk for poor tolerance of cCHRT. Preferably, such parameters should be easily measured and cost-effective with a minimal burden for the patient. Such information can be used by medical specialists for identifying patients who are expected to tolerate cCHRT, which is important for shared decision-making. The aim of this study was to gain insight into the associations between pretreatment physical status parameters and tolerance of cCHRT and survival among patients with stage III NSCLC in everyday clinical practice.

Methods

Study Design

This project concerned a retrospective cohort study for which anonymous data from the medical records from a clinic for radiotherapy were used. All patients who underwent cCHRT for stage III NSCLC between 2006 and 2015 and who had no objection for the use of their usual care data for research purposes were included. Baseline measurements and physical status parameters were usually scheduled on the day of the first irradiation. The internal review board of a clinic for radiotherapy decided that this study met their ethical policies and the regulations of the Dutch government.

Patients and Data Collection

Patients aged ≥ 18 years with stage III NSCLC, who received primary cCHRT between 2006 and 2015 in two teaching hospitals, two non-teaching hospitals or a university medical centre, were included. Clinical tumour staging was performed according to the 7th TNM staging of the International Association for the Study of Lung Cancer [17]. NSCLC was classified as squamous cell carcinoma, adenocarcinoma, large cell carcinoma and not otherwise specified. The following pretreatment patient characteristics and physical status parameters were collected from the electronic patient records: sex, age, body mass index (BMI), fat-free mass index (FFMI), forced expiratory volume in one second (FEV_1), carbon monoxide lung diffusion capacity (DLCO), World Health Organization (WHO) performance status, Charlson comorbidity index and maximal handgrip strength. In addition, prescribed and received radiation dose, date of diagnosis, date of first and last irradiation and date of death or last registration were collected. After data collection, all data were checked for completeness and accuracy.

Treatment Protocol

cCHRT was defined as treatment with chemotherapy and radiotherapy with any overlap between the two modalities. After one or two chemotherapy cycles, radiotherapy was given to the primary tumour and lymph nodes [18]. In the first three weeks, 30 fractions of 1.5 Gy (Gy) were given twice daily, followed by fractions of 2 Gy once daily, with a minimum dose of 54 Gy and a maximum of 69 Gy [19]. A mean radiation dose of 65 Gy delivered to the tumour and affected lymph nodes was given within 5.5 weeks. This corresponds to a biological equivalent of 72 Gy given in 36 daily fractions in 7.2 weeks [20].

Pretreatment Physical Status Parameters

Anthropometry and Body Composition

Bioelectrical impedance analysis (Omron Healthcare Group, Hoofddorp, The Netherlands) with a single-frequency (50 kHz) was used for estimating body composition [21, 22]. Patients were standing with legs apart and arms straight forward, holding the device with both hands. Results are automatically corrected for body height, body mass, Fat-free mass (FFM), sex and age. Body mass index was categorized as underweight (< 18.5 kg/m^2) or normal weight/overweight (≥ 18.5 kg/m^2) [23]. The fat-free mass index FFMI (kg/m^2) is a body height-adjusted assessment of FFM. Low FFMI was defined as a FFMI < 17 kg/m^2 in male patients and < 15 kg/m^2 in female patients, based on 10^{th} percentile values for healthy subjects [24].

Lung Function

FEV_1 and DLCO measurements were performed by a pulmonary function technician and expressed as a percentage of predicted based on sex and age [25]. Using spirometry, patients were asked to breathe in as deeply as possible and then exhale as hard, quickly and long as possible [26, 27]. The DLCO is a medical test that determines how much oxygen travels from the alveoli of the lungs to the blood stream [27]. Scores ≤ 80% of predictive for FEV_1 and DLCO were classified as low [28].

Physical Functioning

The WHO performance status was assessed by the radiation oncologist and used to indicate the level of physical functioning. Patients with a score ≥ 2 were classified as having a poor performance status [29]. The Charlson comorbidity index was extracted from the medical records and classified as none to mild comorbidity (score 0–3) and severe comorbidity (score ≥ 4) [30]. Handgrip strength as an indication of overall muscle strength was measured with a handheld dynamometer (JAMAR Hydraulic Hand Dynamometer, JA Preston Corporation, Jackson, MI, USA) [31]. Patients were seated in a chair with their elbow flexed at 90° and the forearm in the neutral position without any arm support from the chair [32]. A value below the 10^{th} percentile of the UK Biobank reference values, was considered as low handgrip strength [33].

Outcome Variables

Tolerance of cCHRT was classified as 'yes' when the received radiation dose was at least equal to the prescribed radiation dose. Five-year survival was defined as the time

from diagnosis to death of any cause or to date of last follow-up with a maximum of five years. Last date for checking date of death using the local hospital data registration or the Dutch Municipal Personal Records Database was June 1st 2019.

Statistical Analyses

Data were analysed using IBM SPSS Statistics version 24 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics were used to summarize patient characteristics and cross-tabulations were used to analyse associations between pretreatment physical status parameters and tolerance of cCHRT using chi^2 tests ($P < 0.05$ two sided). Univariate and multivariate binary logistic regression analyses were performed for analysing the associations between pretreatment physical status parameters and tolerance of cCHRT. In order to ensure sufficient power, the 'one in ten rule' was applied. The rule states that one predictive variable can be studied for every ten events [34]. In this study, nine associated variables were studied. In case these were all included in multivariable analyses, a minimum number of 90 events should have occurred. Age, sex and pretreatment physical status parameters with a P value < 0.10 in the univariate analyses were selected for the multivariate analyses. The odds ratio (OR) and corresponding 95% confidence interval (CI) was displayed for each parameter. An OR < 1.0 indicated poorer tolerance of cCHRT. Overall survival during a five-year follow-up period was analysed according to Kaplan–Meier, and significant differences between groups were assessed by the log-rank test. Univariate and multivariate hazard ratios (HRs) and 95% CI for associations between physical status parameters and survival were calculated by Cox proportional hazards analyses. Age, sex and pretreatment physical status parameters with a P value < 0.10 in the univariate analyses were selected for the multivariate regression analyses. Poorer survival was indicated by a HR > 1.0. In multivariate analyses (backward conditional method; Pin = 0.10, Pout = 0.10), variables that were significant in univariate analyses were included. It was assumed that the associations between physical status parameters and survival could differ between sex and age groups. Therefore, multivariate analyses for overall survival were also stratified according to sex and age. P values < 0.10 were considered statistically significant.

Results

Data of 577 patients with stage III NSCLC, 357 male patients (61.9%) and 220 female patients (38.1%) with a mean age of 63.6 (standard deviation (SD) 9.2) years receiving cCHRT were available for analysis. In Table 1, baseline characteristics of patients are summarized according to the tolerance of cCHRT. WHO performance status 0–1, normal/overweight and normal handgrip strength were significantly more present among patients who tolerated cCHRT ($P < 0.05$). Due to the high proportion of missing cases, FEV_1 and DLCO were excluded from multivariable analyses (Table1).

Tolerance of cCHRT

A total of 50 patients (8.7%) did not tolerate cCHRT. In univariate regression analyses, patients being underweight had a significantly poorer tolerance of cCHRT compared to patients with normal weight/overweight (OR 0.32). Patients with WHO performance status ≥ 2 had a significantly poorer tolerance of cCHRT compared to patients with WHO performance status 0–1 (OR 0.37). Finally, low handgrip strength was associated with poor tolerance of cCHRT (OR 0.52). In multivariable analyses, being underweight (OR 0.36) and WHO performance status ≥ 2 (OR 0.43) remained significantly associated with poorer tolerance of cCHRT. Results of the univariate and multivariate regression analyses for tolerance of cCHRT are shown in Table 2.

Overall Survival

Median overall survival for the whole group was 23 months, and at the time of analysis after five years, 404 patients (70%) had died. Median overall survival was 23 months for those who tolerated cCHRT and 11 months for those who did not tolerate cCHRT ($P = 0.007$, Fig. 1a). The one-, three- and five-year survival rates for the whole group were 69%, 38% and 30%, respectively. In univariate analyses, age (HR 1.23), male sex (HR 1.24), low FFMI (HR 1.27), DLCO < 80% (HR 1.42), WHO performance status ≥ 2 (HR 1.91), low handgrip strength (HR 1.32) and cCHRT intolerance (HR 1.56) were significantly associated with poorer survival. The following factors were analysed for their association with survival in multivariable analyses: age, sex, FFMI, WHO performance status, handgrip strength and tolerance of cCHRT were analysed for their association with survival in multivariable analyses. Age ≥ 70 years (HR 1.22), WHO performance status ≥ 2 (HR 1.73), low FFMI (HR 1.23) and cCHRT intolerance (HR 1.55) remained significantly associated with poor survival. The results of univariate and multivariate Cox regression analyses for survival are shown in Table 3.

Overall Survival Stratified for Sex and Age

Median overall survival was significantly lower in male patients compared to female patients (21 versus 26 months; $P = 0.037$; Fig. 1b). In male patients, WHO

Table 1 Pretreatment patient characteristics and physical status parameters according to tolerance of cCHRT

Variable, number (%)	Tolerance of cCHRT		
	No[a] ($n=50$)	Yes[b] ($n=527$)	*P* value
Age (years)	63.9 ± 8.9 (45 to 80)	63.5 ± 9.2 (32 to 85)	
< 70 years	35 (70.0)	368 (69.8)	0.98
≥ 70 years	15 (30.0)	159 (30.2)	
Sex			
Male	35 (70.0)	322 (61.1)	0.22
Female	15 (30.0)	205 (38.9)	
Histology			
Adenocarcinoma	15 (30.0)	139 (26.4)	0.47
Squamous cell carcinoma	20 (40.0)	173 (32.8)	
Large cell carcinoma	4 (8.0)	82 (15.6)	
Non-small cell lung cancer	9 (18.0)	120 (22.8)	
No histological diagnosis	2 (4.0)	13 (2.5)	
WHO performance status			
0–1	43 (86.0)	478 (90.7)	0.02[e]
≥ 2	7 (14.0)	29 (5.5)	
Unknown	0 (0.0)	20 (3.8)	
Charlson comorbidity index			
0–3	25 (50.0)	299 (56.7)	0.36
≥ 4	25 (50.0)	228 (43.3)	
BMI			
Underweight (< 18.5 kg/m^2)	7 (14.0)	26 (4.9)	0.01
Normal/overweight (≥ 18.5 kg/m^2)	43 (86.0)	501 (95.1)	
FFMI			
Normal FFMI	35 (70.0)	395 (75.0)	0.52[e]
Low FFMI[c]	13 (26.0)	118 (22.4)	
Unknown	2 (4.0)	14 (2.7)	
Handgrip strength			
Normal	36 (72.0)	430 (81.6)	0.05[e]
Low[d]	13 (26.0)	80 (15.2)	
Unknown	1 (2.0)	17 (3.2)	
FEV_1			
< 80% of predicted	25 (50.0)	191 (36.2)	0.18[e]
≥ 80% of predicted	20 (40.0)	233 (44.2)	
Unknown	5 (10.0)	109 (19.5)	
DLCO			
< 80% of predicted	32 (64.0)	278 (52.8)	0.44[e]
≥ 80% of predicted	9 (18.0)	106 (20.1)	
Unknown	9 (18.0)	143 (27.1)	

Data are presented as mean ± SD or n (%)

BMI body mass index, *DLCO* diffusing capacity for carbon monoxide, *FEV_1* forced expiratory volume in 1 s, *FFMI* fat-free mass index, *SD* standard deviation, *WHO* World Health Organization

[a]No: received radiation dose was less than the prescribed radiation dose

[b]Yes: received radiation dose was at least equal to the prescribed radiation dose

[c]Males FFMI < 17 kg/m^2 and females < 15 kg/m^2

[d]< 10th percentile of established normative values (35)

[e]Chi^2 test was calculated without missing values

Table 2 Univariate and multivariate odds ratios for associations of pretreatment patient characteristics and physical status parameters with tolerance of cCHRT in patients with stage III NSCLC

	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age				
< 70 years	Reference	0.98	NS	
≥ 70 years	1.01 (0.54 to 1.90)			
Sex				
Male	0.67 (0.36 to 1.26)	0.22	NS	
Female	Reference			
WHO performance status				
0–1	Reference	0.03	Reference	0.07
≥ 2	0.37 (0.15 to 0.90)		0.43 (0.17 to 1.07)	
Charlson comorbidity index				
0–3	Reference	0.36	NI[c]	
≥ 4	0.76 (0.43 to 1.36)			
BMI				
Underweight (< 18.5 kg/m^2)	0.32 (0.13 to 0.78)	0.01	0.36 (0.15 to 0.90)	0.03
Normal /overweight (≥ 18.5 kg/New normative values for handgrip strength: results from the UK Biobankm^2)	Reference		Reference	
FFMI				
Normal FFMI	Reference	0.52	NI[c]	
Low FFMI[b]	0.80 (0.41 to 1.57)			
Handgrip strength				
Normal	Reference	0.06	NS	
Low[c]	0.52 (0.26 to 1.02)			
FEV_1				
< 80% of predicted	0.66 (0.35 to 1.22)	0.18	NI[c]	
≥ 80% of predicted	Reference			
DLCO				
< 80% of predicted	0.74 (0.34 to 1.60)	0.44	NI[c]	
≥ 80% of predicted	Reference			

BMI body mass index; *cCHRT* concurrent chemoradiation; *CI* confidence interval; *DLCO* diffusing capacity for carbon monoxide; *FEV1* forced expiratory volume in 1 second; *FFMI* fat-free mass index; NI=not included; NS=not significant; *NSCLC* non-small cell lung cancer; *OR* odds ratio; *WHO* World Health Organization

[a]Not included when P-value ≥0.10

[b]Males FFMI <17 kg/m^2 and females FFMI<15 kg/m^2

[c]<10th percentile of established normative values [33]

performance status ≥ 2 (HR 1.54), low FFMI (HR 1.60) and cCHRT intolerance (HR 1.85) were significantly associated with worse survival, whereas in female patients only WHO performance status ≥ 2 (HR 2.56) was significantly associated with worse survival (Table 4). Median overall survival was 24 months for patients aged < 70 years and 19 months for those aged ≥ 70 years ($P = 0.050$; Fig. 1c). In patients aged < 70 years, WHO performance status ≥ 2 (HR 1.81), low handgrip strength (HR 1.47) and cCHRT intolerance (HR 1.89) were significantly associated with worse survival, whereas in patients aged ≥ 70 years, only age per year as a continuous variable (HR 1.07) and low FFMI (HR 1.60) were significantly associated with worse survival (Table 4).

Discussion

Results from this study demonstrated that several physical status parameters were associated with outcome following cCHRT. In total, 8.7% of the patients did not tolerate cCHRT, especially those with poor WHO performance status or BMI < 18.5 kg/m^2. Physical status parameters and tolerance of cCHRT were also associated with survival;

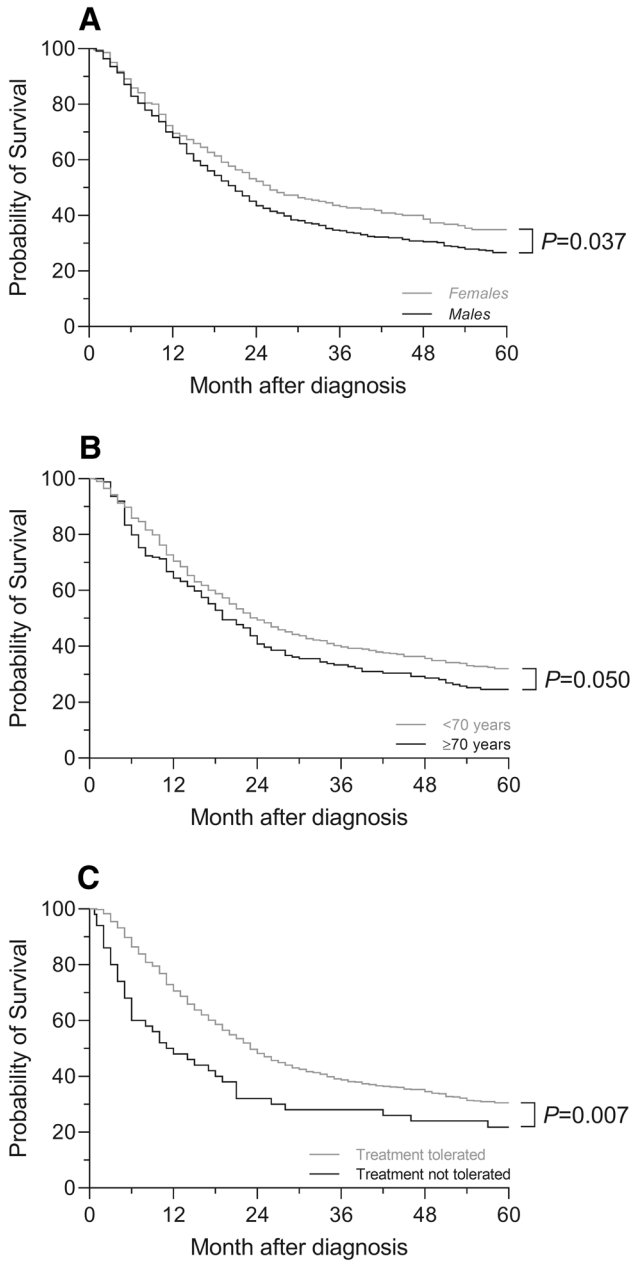


Fig. 1 Kaplan–Meier survival curves. **a** Kaplan–Meier survival curve according to sex in non-small cell lung cancer patients receiving concurrent chemoradiation (Log rank: $P=0.04$). **b** Kaplan–Meier survival curve according to age groups in non-small cell lung cancer patients receiving concurrent chemoradiation (Log rank: $P=0.05$). **c** Kaplan–Meier survival curve according to tolerance of cCHRT in non-small cell lung cancer patients receiving concurrent chemoradiation (Log rank: $P=0.01$)

however, associations differed between males and females and between younger and older patients.

A BMI < 18.5 kg/m^2 and poor WHO performance status were independently associated with poor tolerance of cCHRT. Studies investigating the relationship between WHO performance status and tolerance of cCHRT in lung cancer are lacking. Furthermore, one study indicated that malnutrition, especially in overweight patients, negatively influences survival of stage III NSCLC [35]. Although significance disappeared in multivariable analyses, low handgrip strength also seemed to be associated with poorer tolerance of cCHRT. This is in line with previous studies which have shown an association between low handgrip strength before treatment and an increased risk of poor treatment tolerance in patients with oesophageal and colorectal cancer [36–38]. Results of the current study and previous studies therefore suggest that BMI < 18.5 kg/m^2, poor WHO performance status and low handgrip strength before treatment might have an added value in identifying patients at high risk of poor tolerance of cCHRT.

Additionally, poor tolerance of cCHRT was most significantly associated with poorer survival, even after adjustment for patient characteristics. These findings suggest that it is important to identify which patients are expected to benefit from this radical treatment with cCHRT for discussing the balance between quality of life and survival with patients. Low FFMI, poor WHO performance status and low handgrip strength were significantly associated with worse survival; however, associations differed between males and females and between younger and older patients. A previous study showed an association between low FFMI, poor WHO performance status and low handgrip strength and worse survival in patients with NSCLC [39, 40]. In previous research [41], the prognostic value of low DLCO to predict worse survival in Japanese patients with stage III NSCLC has also been indicated. Although these results were also shown in univariate analyses in the current study, unfortunately DLCO could not be included in multivariable analyses due to missing values. Future studies should focus on this promising parameter.

Poor WHO performance status, low FFMI and not tolerating cCHRT were significantly associated with poorer survival in male patients, whereas this was only poor WHO performance status in female patients. These differences might be explained by the small number of female patients in this study, resulting in a lack of statistical power. In patients < 70 years, poor WHO performance status, low handgrip strength and not tolerating cCHRT were significantly associated with poorer survival. In older patients, age (as a continuous variable) and low FFMI were significantly associated with poorer survival. It is plausible that relatively fit older patients aged ≥ 70 years were selected for cCHRT in this observational study in everyday clinical practice, which means that numbers of vulnerable older patients might have been too small for reaching significance [5].

Physical status parameters are often associated with treatment intolerance and worse survival in patients with cancer, especially in those undergoing surgery [43, 44]. Despite this,

Table 3 Univariate and multivariate hazard ratios and 95% CI for associations between physical status parameters and survival in patients with stage III NSCLC

	Median survival (months)	Univariate		Multivariate without tolerance of cCHRT		Multivariate with tolerance of cCHRT	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age							
< 70 years	24	Reference	0.05	Reference	0.05	Reference	0.08
≥ 70 years	19	1.23 (0.98 to 1.51)		1.24 (1.00 to 1.54)		1.22 (0.98 to 1.51)	
Sex							
Male	21	1.24 (1.01 to 1.52)	0.04	NS		NS	
Female	26	Reference					
WHO performance status							
0–1	24	Reference	≤ 0.01	Reference	≤ 0.01	Reference	≤ 0.01
≥ 2	10	1.91 (1.33 to 2.74)		1.77 (1.23 to 2.57)		1.73 (1.19 to 2.51)	
Charlson comorbidity index							
0–3	21	Reference	0.31	NI[a]		NI[a]	
≥ 4	23	1.11 (0.91 to 1.35)					
BMI							
Underweight	15	1.28 (0.85 to 1.92)	0.23	NI[a]		NI[a]	
Normal/overweight	23	Reference					
FFMI							
Normal FFMI	24	Reference	0.04	Reference	0.07	Reference	0.08
Low FFMI[b]	21	1.27 (1.02 to 1.56)		1.24 (0.98 to 1.57)		1.23 (0.97 to 1.56)	
Handgrip strength							
Normal	23	Reference	0.03	NS		NS	
Low[c]	17	1.32 (1.02 to 1.70)					
FEV_1							
< 80% of predicted	21	1.13 (0.91 to 1.40)	0.28	NI[a]		NI[a]	
≥ 80%	23	Reference					
DLCO[f]							
< 80%	21	1.42 (1.09 to 1.85)	0.01[e]	NI[a]		NI[a]	
≥ 80%	29	Reference					
Tolerance of cCHRT							
No[d]	11	1.56 (1.12 to 2.18)	0.01	NI[a]		1.55 (1.11 to 2.17)	0.01
Yes[e]	23	Reference				Reference	

BMI body mass index, *cCHRT* concurrent chemoradiation, *CI* confidence interval, *DLCO* diffusing capacity for carbon monoxide; *FEV1* forced expiratory volume in 1 s, *FFMI* fat-free mass index, *HR* hazard ratio, *NI* not included, *NS* not significant, *NSCLC* non-small cell lung cancer, *WHO* World Health Organization

[a]Not included when *P*-value ≥ 0.10

[b]Males FFMI < 17 kg/m^2 and females FFMI < 15 kg/m^2

[c]< 10th percentile of established normative values [33]

[d]No = received radiation dose was less than the prescribed radiation dose

[e]Yes = received radiation dose was at least equal to the prescribed radiation dose

[f]DLCO was not included in multivariate analysis because of a high percentage of missing cases (26.3%) and because of violating the proportional hazards assumption

the association between a combination of these pretreatment physical status parameters and tolerance of cCHRT and survival among patients with stage III NSCLC has not been investigated before. The large sample size in this population truly reflected clinical practice and quality and completeness of included data was high, except for DLCO. Using real-world data means that patients who were sufficiently fit for cCHRT were included as advised by European guidelines. [45, 46]. Because of this possible selection bias, results for the associations between pretreatment physical performance parameters and tolerance of CHRT might differ for vulnerable patients. This study demonstrates that pretreatment physical status

Table 4 Multivariate hazard ratios without and with treatment tolerance for associations of pretreatment patient characteristics and physical status parameters with tolerance of cCHRT and survival in patients with stage III NSCLC stratified for sex and age

	Multivariate without treatment tolerance				Multivariate with treatment tolerance			
	Male		Female		Male		Female	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age								
< 70 years	Reference	0.08	NS		NS		NS	
≥ 70 years	1.26 (0.97 to 1.63)							
WHO performance status								
0–1	NS		Reference	≤ 0.01	Reference	0.07	0.07	≤ 0.01
≥ 2			2.56 (1.38 to 4.76)		1.54 (0.97 to 2.42)		2.56 (1.38 to 4.76)	
FFMI								
Normal FFMI	Reference	≤ 0.01	NS		Reference	≤ 0.01	NS	
Low FFMI[a]	1.65 (1.24–2.21)				1.60 (1.19 to 2.14)			
Handgrip strength								
Normal	NS		NS		NS		NS	
Low[b]								
Tolerance of cCHRT								
No[c]	NI[e]		NI[e]		1.85 (1.24 to 2.77)	≤ 0.01	NS	
Yes[d]					Reference			
	Age < 70 years		Age < 70 years		Age < 70 years		Age < 70 years	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, continuous per year	NS		1.07 (1.01 to 1.13)	0.02	NS		1.07 (1.01 to 1.13)	0.02
Sex								
Male	NS		NS		NS		NS	
Female								
WHO performance status								
0–1	Reference	0.02	NS		Reference	0.02	NS	
≥ 2	1.76 (1.09 to 2.84)				1.81 (1.12 to 2.92)			
FFMI								
Normal FFMI	NS		Reference	0.02	NS		Reference	0.02
Low FFMI[a]			1.60 (1.08 to 2.39)				1.60 (1.08 to 2.39)	
Handgrip strength								
Normal	Reference	0.01	NS		Reference	0.02	NS	
Low[b]	1.52 (1.09 to 2.12)				1.47 (1.06 to 2.06)			
Tolerance of cCHRT								
No[c]	NI[e]		NS		1.89 (1.26 to 2.82)	≤ 0.01	NS	
Yes[d]					Reference			

cCHRT concurrent chemoradiation, *CI* confidence interval, *FFMI* fat-free mass index, *HR* hazard ratio, *NI* not included, *NS* not significant, *NSCLC* non-small cell lung cancer, *WHO* World Health Organization

[a]Males FFMI < 17 kg/m^2 and females FFMI < 15 kg/m^2

[b]< 10th percentile of established normative values [33],

[c]No = received radiation dose was less than the prescribed radiation dose,

[d]Yes = received radiation dose was at least equal to the prescribed radiation dose,

[e]Not included as *P* value ≥ 0.10

parameters are associated with both tolerance of cCHRT and survival. However, in elderly patients, the impact of toxicities on quality of life (especially preserving independency) may be just as important as the prolongation of life expectancy. Future evidence on the associations between pretreatment physical status parameters and quality of life and functional recovery is essential to make adequate treatment decisions with patients. In addition, physical tests might also be used

to identify high-risk patients who might benefit from lifestyle interventions before and during cancer treatment [47]. Another limitation of this study is the lack of patient-related parameters such as nutritional status, psychological distress and social support. These important functional status parameters are recommended by the American Society of Clinical Oncology (ASCO) guidelines for older and/or more vulnerable patients receiving chemotherapy [42]. It is important to know the rate of adverse events in order to determine the definition of poor treatment tolerance. Ideally, this is derived from both the dose intensity of radiotherapy and the dose intensity for chemotherapy. Unfortunately, the latter was not available in the database from the clinic for radiotherapy. It is recommended to include this information in a subsequent study. Furthermore, it would be useful to determine whether these physical status parameters are also associated with treatment tolerance in stage III NSCLC patients undergoing less aggressive treatment, such as immunotherapy.

In conclusion, in patients with stage III NSCLC receiving cCHRT, poor WHO performance status and BMI < 18.5 kg/m^2 were independently associated with tolerance of cCHRT, and both physical status parameters and intolerance of cCHRT were independently associated with poorer survival. Treatment selection for patients with stage III NSCLC is already well underway. Further improvements may be established by paying attention to the risk of intolerance of cCHRT, which increases the patient's risk of death and decreases quality of life. Optimizing physical status in patients at risk for intolerance of cCHRT can be a next step for improving treatment outcomes.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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