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The prognostic value of early onset, CT derived loss of muscle and adipose tissue during chemotherapy in metastatic non-small cell lung cancer

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ABSTRACT

Objectives: To evaluate the relationship between early changes in muscle and adipose tissue during chemotherapy and overall survival (OS) in stage IV non-small cell lung cancer (NSCLC).
Materials and methods: In this post-hoc analysis of the first line NVALT12 trial (NCT01171170) in stage IV NSCLC, skeletal muscle (SM), radiation attenuation (RA), subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) were assessed at the third lumbar level on CT-images obtained before initiation of chemotherapy and shortly after administration of the second cycle. The contribution of changes in different body compartments to overall survival was assessed.
Results: CT scans of 111 patients were included. Analysis of body composition changes between the baseline and the follow-up scan, revealed that overall SM cross sectional area (CSA), radiation attenuation and SAT CSA decreased respectively by $-1.2 \pm 2.9\,cm^2/m^2$ ($p < 0.001$), -0.7 ± 3.3 HU ($p = 0.026$) and $-1.9 \pm 8.7\,cm^2/m^2$ ($p = 0.026$), while no significant changes in VAT tissue were observed. Longitudinally, median OS was significantly shorter among patients losing SM compared to patients with preserved SM (9.4 versus 14.2 months; HR 1.9, 95% CI: 1.23, 2.79, $p = 0.003$). Multivariate analyses showed that proportional loss of muscle mass was associated with poor OS (HR 0.949, 95% CI: 0.915, 0.985, $p = 0.006$) independent from important clinical prognostic factors including WHO-PS, gender, age and Charlson comorbidity index.
Conclusion: Early loss of SM during first line chemotherapy is a poor prognostic factor in stage IV NSCLC patients. Future studies have to reveal whether early supportive intervention guided by initial CT muscle response to chemotherapy can influence the wasting process and related mortality risk.

1. Introduction

Despite recent developments in cancer diagnostics and treatment modalities, mortality rates maintain high in non-small cell lung cancer (NSCLC) [1]. One of the factors contributing to high mortality rates is progressive unintentional weight loss of body weight and muscle mass (i.e. cachexia [2].

Computed tomography (CT) has emerged as a promising tool in assessment of cancer cachexia. CT scans are routinely acquired in cancer patients for disease diagnosis, staging and treatment follow-up and thereby readily available from medical records to extract body composition data. Skeletal muscle- and adipose tissue depletion, both

Abbreviations: CI, confidence interval; CSA, cross-sectional area; CT, computed tomography; FDG, fluorodeoxyglucose; HR, hazard ratio; HU, Hounsfield units; L3, third lumbar level; N, number; NSCLC, non-small cell lung cancer; OS, overall survival; PET, positron emission tomography; RA, radiation attenuation; SAT, subcutaneous adipose tissue; SM, skeletal muscle; SMI, skeletal muscle index; VAT, visceral adipose tissue; WHO PS, World Health Organisation Performance status

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characteristics of cachexia [3], are clinically important as predictors of cancer outcomes [4–6]. Cachexia is frequently observed in lung cancer [7] and low skeletal muscle mass at presentation has been linked to functional deterioration, chemotherapy intolerance, and poor survival rates [8–10].

Muscle tissue is plastic, undergoing constant remodelling in response to anabolic and catabolic signals related to a.o. aging [11], exercise [12], malnutrition [13] inflammation [14] and drug interventions [15]. Evidence from experimental research suggests that chemotherapy might contribute to muscle wasting, via activation of nuclear factor kappa B and upregulation of myostatin [16]. Thereby, even weight stable patients with normal muscle mass before therapy initiation might lose muscle mass during the course of treatment [17].

To date, a few longitudinal studies addressed changes in muscle mass during anti-tumour therapy in NSCLC. In 35 stage IV NSCLC patients treated with palliative chemotherapy, muscle mass loss was observed in half of the study population over the duration of chemotherapy (approximately 9 weeks). However, the authors found no significant survival effect in univariate analysis [18]. Another small study reported muscle depletion in 30 stage III and IV NSCLC patients, which was accompanied by physical functional decline. The prognostic effect of muscle depletion was not examined [19].

Next to skeletal muscle depletion, cachexia often also effects other tissues, including adipose tissue. Although adipose tissue mass has been emerging as a prognostic factor, results to date are confusing. Patients with low baseline subcutaneous adipose tissue in gastrointestinal- and lung cancer [20] or low visceral adipose tissue in renal cell carcinoma exhibited lower survival rates [21]. In contrast, high adipose infiltration in the skeletal muscle as a measure of muscle quality, reflected on CT analysis by low skeletal muscle radiodensity, was associated with shorter overall survival and shorter disease free survival in patients with various other cancer types [5,22–25].

The prognostic value of early onset changes in muscle- and adipose tissue compartments in therapy naïve NSCLC patients during chemotherapy is lacking. Particularly, in this patient population known for poor survival rates, timely information on body compartment changes could be of clinical relevance for patient guidance and treatment decision making. Therefore, the primary goal of our study is to evaluate early body composition changes in relation to survival in therapy naïve metastatic NSCLC patients undergoing chemotherapy.

2. Material and methods

2.1. Study population and study design

This study was a post-hoc analysis of a multicentre randomized phase II trial investigating the effect on survival of nitroglycerin patches added to paclitaxel-carboplatin-bevacizumab in 223 therapy naïve patients with stage IV non-squamous NSCLC (NCT01171170). The full and detailed methodology and results of this study has been published previously [26].

In short, patients were randomized between paclitaxel-carboplatin-bevacizumab with (experimental arm) and without nitroglycerin patches (control arm). Adding nitroglycerin to first-line carboplatin-paclitaxel-bevacizumab did not improve progression-free survival and overall survival (OS) in patients with stage IV non-squamous NSCLC. Exploratory endpoint of the study was to assess whether nitroglycerin was related with an early decrease in 18 F-fluorodeoxyglucose (18 F-FDG) uptake. According to the protocol, a second 18 F-FDG positron emission tomography (PET) scan combined with CT scan was assessed for patients with a baseline PET/CT after the second cycle of chemotherapy [27], with median follow-up time of 23 (17–50) days between follow-up scan and initiation of therapy. Specific patient characteristics (age, gender, WHO PS, smoking status, histology, BMI and Charlson comorbidity index) were selected from patient records [28]. Patients were selected from this study because the population is a well–defined randomized cohort in which all patients have received a homogenous standardized chemotherapeutic regime. Next to this, all patients were assessed by a physician with follow-up scans at pre-determined time points.

2.2. Image analysis

In this post-hoc analysis body composition was analysed on low dose CT scan by assessment of the cross-sectional area (CSA) at the third lumbar level by two assessors. CSA of skeletal muscle, subcutaneous adipose tissue and visceral adipose tissue were analysed with Slice-O-Matic software v5.0 (Tomovision, Montreal, Canada). One image in each scan was selected. During anatomical land marking, the first image at the third lumbar level with both vertebral transverse processes clearly visible was used for analysis. CSA of these structures were quantified based on pre-established thresholds of Hounsfield units (skeletal muscle -29 to 150, subcutaneous adipose tissue -190 to -30, and visceral adipose tissue -150 to -50). Boundaries were corrected manually when necessary.

Baseline CSA was normalised for height in meters squared and reported in cm^2/m^2. Changes in CSA between CT scans were expressed as a percentage. We found a mean coefficient of variation between observers of 1.3% for skeletal muscle area, subcutaneous- and visceral adipose tissue in a random sample of 15 patients, which is in line with a variation of 0–2% in other studies [7,29–31]. Therefore, a measurement error of 1.3% was adopted. Changes of equal or larger than −1.3% were considered as 'loss of tissue', while changes of smaller than -1.3% were considered 'maintenance of tissue'. Furthermore, skeletal muscle radiation attenuation was assessed as the average housefield units (HU) of the total skeletal muscle area within the range -29 to 150 HU (i.e. excluding intramuscular adipose tissue).

2.3. Study endpoints and statistical analyses

Patients were included if CT scans both at baseline and follow-up were available, were assessed within 3 weeks after the second chemotherapy and contained images of the third lumbar level. Descriptive statistics of demographic and clinical variables were obtained. Means (± SD) were provided for continuous normally distributed variables, median (range) for continuous not-normally distributed variables and percentages were shown for categorical variables. Comparisons within groups were performed with paired *t*-test and between groups with an independent *t*-test.

The primary endpoint of this study was OS. OS was defined as the interval from randomization to death from any cause. The probabilities of OS were calculated using the Kaplan-Meier method. Survival curves of patients with and without skeletal muscle loss were tested for significance using the log-rank test. To assess the contribution of different body compartments to OS, multivariate Cox regression analysis was performed with body composition changes, gender, age, Charlson comorbidity index, and BMI as independent variables. Variables were tested for interactions. In this study population the ECOG performance score was between 0–1 in 97.5 percent of the patients and therefore not included in the regression analysis. Proportional hazard assumption was tested using visual inspection of log-minus-log survival plots. All analyses were performed using SPSS statistical software (SPSS Statistics for Windows, Version 24.0, IBM, Armonk, NY). Results with two-sided exact *p* values (≤ 0.05) were considered statistically significant.

3. Results

3.1. Patients and characteristics

CT scans from 111 of the 223 enrolled patients were eligible (CONSORT Fig. 1). Baseline patient characteristics are shown in Table 1.

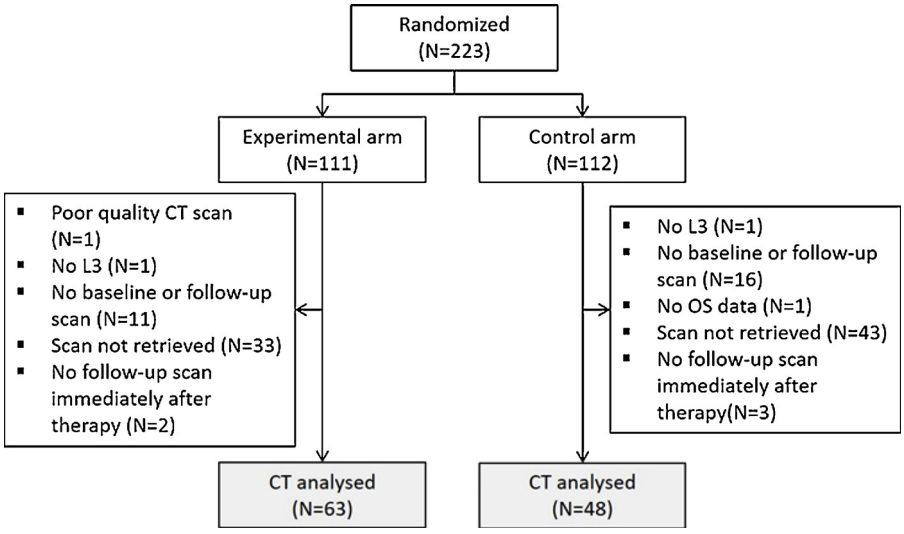

Fig. 1. Consort.

Table 1
Patient characteristics (N = 111).

Experimental arm/control arm, N	63 / 48
Male/Female, N	60 / 51
Age (mean, range)	61 (39, 79)
WHO – PS, N (%)	
0	50 45.0)
1	46 (41.1)
2	3 (2.7)
Missing = 12	
Pre-existent comorbidity, N (%)	
COPD	16 (14.4)
Cardio - vascular	41 (36.9)
Diabetes Mellitus	12 (10.8)
Gastro - intestinal	15 (13.5)
> 1 co-morbidity	50 (45%)
Smoker, N (%)	
Current	48 (43.2)
Ex	49 (44.1)
Never	14 (12.6)
Histology, N (%)	
Adenocarcinoma	96 (86.5)
Large cell	6 (5.4)
Other	7 (6.4)
Missing = 2	
Body weight, kg	74.1 ± 14.7
BMI, kg/m^2	25.0 ± 4.3

Definition of abbreviations: WHO PS = World Health Organization Performance Score.
BMI = body mass index.
Data are represented as mean ± SD or median (range), unless stated otherwise.
Mutation status of the patients was not available.

3.2. Body composition

Table 2 shows baseline measurements and body composition changes parameters of the whole group. In total 65 (58.5%) lost muscle mass during the course of chemotherapy. Analysis of body composition changes between the baseline and the follow-up scan revealed that muscle CSA, radiation attenuation and subcutaneous adipose tissue CSA decreased respectively by -1.2 ± 2.9 cm^2/m^2 ($p < 0.001$), -0.7 ± 3.3 HU ($p = 0.026$) and -1.9 ± 8.7 cm^2/m^2 ($p = 0.026$), while no significant changes in visceral adipose tissue were observed.

3.3. Survival

Median OS (95% confidence interval [CI]) was similar between subjects with normal versus low skeletal muscle index at baseline (12.2 months, 95% CI: 9.8, 14.7 versus 10.3 months, 95% CI: 7.8, 12.7, hazard ratio 1.1, 95% CI: 0.8, 1.7, $p = 0.496$ [data not shown]).

Longitudinally, median OS was significantly shorter among patients losing skeletal muscle mass compared to patients with preserved skeletal muscle mass (9.4 months, 95% CI: 7.1, 11.6 versus 14.2 months, 95% CI: 11.3, 17.1, HR 1.9, 95% CI: 1.23, 2.79, $p = 0.003$) (Fig. 2). Multivariate analyses showed that proportional loss of muscle mass (HR 0.949, 95% CI: 0.915, 0.985, $p = 0.006$) was associated with poor OS independent from important clinical prognostic factors including WHO-PS, gender, age and Charlson comorbidity index. (Table 3).

3.4. Adipose tissue compartments

On multivariate analysis, changes in skeletal muscle mass were associated with OS (Table 3). We therefore stratified patients in two groups; 'maintenance of skeletal muscle mass' and 'loss of skeletal muscle mass'. At baseline, there were no differences between groups regarding weight and body composition. Furthermore, groups did not differ in tumour progression (data not shown). Muscle loss was accompanied by a generalized loss of tissue as both subcutaneous fat and visceral fat decreased. Furthermore, radiation attenuation decreased, which could reflect gain in intramuscular fat (Table 4) [32].

4. Discussion

In the current study, we identified body composition changes after two cycles of chemotherapy treatment initiation in stage IV NSCLC patients. Skeletal muscle CSA, muscle radiation attenuation and to lesser extent subcutaneous adipose tissue decreased throughout treatment indicating a rapid loss in muscle mass and quality. Sixty-nine percent of the patients lost muscle mass and exhibited worse survival rates compared to those with preserved muscle mass.

Next to loss of muscle mass a rapid decline in skeletal muscle radiation attenuation was observed during the course of treatment. Reduced radiation attenuation is believed to reflect fat infiltration (myosteatosis) in the muscle [33]. Myosteatosis in the muscle has indeed been observed in muscle biopsies from cancer patients and was more aggravated in those with weight loss [34]. The phenomenon of myosteatosis is shown in several patients groups including both obese patients [35] and patients with low BMI. This suggests that high muscle

Table 2
Body composition at baseline and change during therapy.

	Baseline	Change, absolute	Change, percentage	*p* value change
Skeletal muscle CSA, $cm^2/m2$	44.4 ± 6.9	−1.2 ± 2.9	−2.7 ± 6.6	< **0.001**
Radiation attenuation (HU)	31.5 ± 7.2	−0.7 ± 3.3	−1.9 ± 12.2	**0.026**
Subcutaneous adipose tissue CSA, $cm^2/m2$	54.5 ± 31.8	−1.9 ± 8.7	−2.1 ± 20.2	**0.026**
Visceral adipose tissue CSA, $cm^2/m2$	34.3 ± 22.5	0.6 ± 8.0	2.1 ± 29.3	0.438

Definition of abbreviations: CSA = cross-sectional area, HU = hounsfield units.
Data are represented as mean ± SD.

fat infiltration is not merely a result of disturbed energy balance but could be driven by disturbances in muscle oxidative metabolism.

A recent study, comparing changes in skeletal muscle during treatment with chemotherapy or targeted therapy (EGFR or ALK TKI) showed significant differences in the loss of skeletal muscle in advanced NSCLC patient [36]. Skeletal muscle was decreased in both groups, but the loss of muscle mass was significantly lower in the targeted therapy group compared to chemotherapy.

In this study, all patients were treated with the same chemotherapeutic regimen (carboplatinum, paclitaxel, bevacizumab). Therefore, it is interesting to speculate about the influence of anti-cancer drugs and toxicity on skeletal muscle changes in advanced NSCLC. From experimental research, it is known that chemotherapy can directly affect regulation of muscle maintenance, possibly mediated by NF-kB activation [37]. Cisplatin is known to induce NF-kB, which triggers muscle wasting. In addition, also the tumour itself is able to increase NF-kB. Thereby, muscle wasting might be both tumor- and chemotherapy induced via common pathways mediated by NF-kB. In this study, nineteen (17%) of the patients experienced an adverse event graded with a CTCAE of ≥ 3. There was no significant difference in toxicity between the group “muscle loss” and “muscle maintenance”. The underlying mechanism why some patients experience chemotherapy-induced muscle wasting, while others maintain muscle mass is unknown.

The added value of the current study is that also in patients receiving standardized chemotherapy, clinically relevant inter-individual responses in body composition were observed (46 patients maintained muscle mass and had a stable body weight) which may partly be reversible by early supportive interventions. Importantly in this context and in contrast to some previous studies [4,6,9,10,25] we did not show that low muscle mass and attenuation at baseline were prognostic for overall survival.

Table 3
Multivariate analysis for predictors of overall survival.

Variable	Multivariate		
	HR	95% CI	*p* value
Δ Muscle mass (%)	0.949	0.915, 0.985	**0.006**
Age (years)	1.008	0.978, 1,039	0.593
Gender	1.593	0.915, 2,772	0.100
WHO PS	1.084	0.847, 1.387	0.520
Charlson comorbidity index	1.132	0.960, 1.335	0.139

The main strength of our study comes from the well-defined randomized patient cohort, receiving a standardized chemotherapeutic regime [26]. However, this study is not without limitations. All patients were treated with the same chemotherapeutic agents however in 63 of 111 patient nitroglycerine patches were added to the therapy. No difference in OS between the two groups was found [26]. The follow-up CT scans were executed according to the protocol on predefined times, CT scans were performed in different medical centres, whereby minor variation in scanning procedure between hospitals and quality of the images cannot be ruled out. Additionally, data on pre-treatment weight

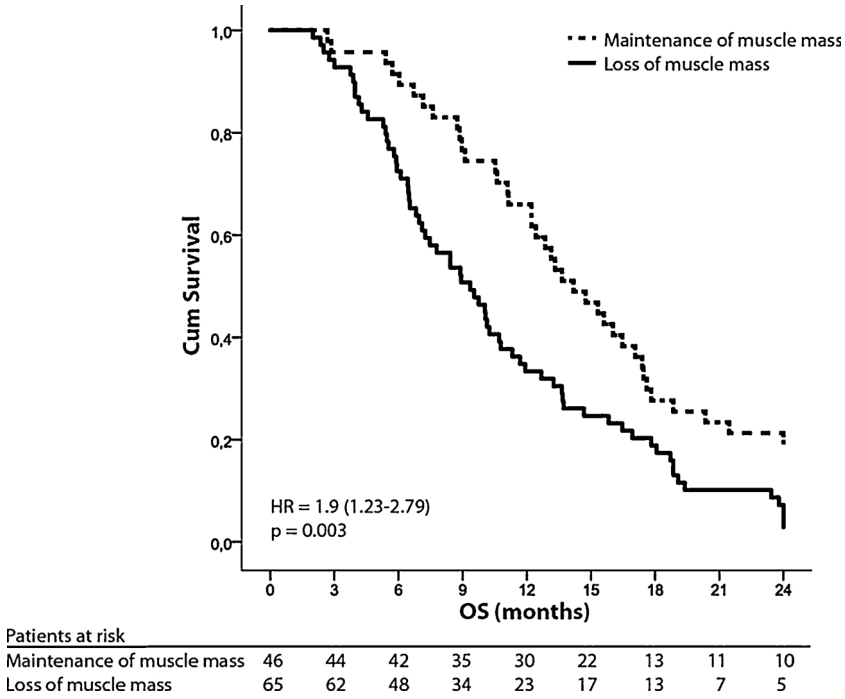

Fig. 2. Kaplan Meier overall survival curve for patients with loss of muscle mass compared to patients without loss of muscle mass.

Table 4
Characterization of the overall wasting pattern in groups stratified by muscle response.

	Maintenance of muscle mass (n = 46)			Loss of muscle mass (n = 65)				
	Baseline	Change, percentage	Within group *p*-value	Baseline	Change, percentage	Within group *p*-value	Between group baseline	Between group change
Skeletal muscle CSA, cm^2/m^2	43.8 ± 6.9	**2.9** ± 4.0	< **0.001**	44.9 ± 7.0	−**6.6** ± 5.1	< **0.001**	0.392	< **0.001**
Radiation attenuation (HU)	30.6 ± 7.6	−0.3 ± 11.9	0.600	32.1 ± 6.9	−**3.0** ± 12.4	**0.015**	0.243	0.233
Subcutaneous adipose tissue CSA, cm^2/m^2	58.3 ± 35.2	7.9 ± 18.5	**0.043**	51.9 ± 29.1	−9.3 ± 18.3	< **0.001**	0.291	< **0.001**
Visceral adipose tissue CSA, cm^2/m^2	36.4 ± 24.6	**11.0** ± 23.4	**0.004**	32.8 ± 21.1	−**4.1** ± 31.5	**0.029**	0.445	**0.006**
Weight, kg	74.7 ± 15.7	0.7 ± 2.4	0.068	73.7 ± 14.1	−**1.7** ± 3.2	< **0.001**	0.811	< **0.001**

Definition of abbreviations: CSA = cross-sectional area, HU = hounsfield units, Data are represented as mean ± SD.

loss were unavailable.

To conclude, this study shows prognostic value of body composition changes after two cycles of chemotherapy treatment in stage IV NSCLC patients. Therefore, CT derived assessment of body composition may provide an additional tool for the treating physician to judge disease severity and related prognosis. Future studies have to reveal whether early supportive intervention, for example with intensive nutritional support, guided by initial CT muscle response to chemotherapy can influence the systemic consequences of NSCLC (treatment) and related elevated mortality risk.

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Conflict of interest statement

J.H.R.J. Degens, K.J.C. Sanders, E.E.C. de Jong, A.M.W.J. Schols: no conflict of interest.

H.J.M. Groen: Dr. Groen reports other from Pfizer, other from Novartis, other from Bristol Meyer Squibb, other from MSD Oncology, other from Eli Lilly, other from Abbvie, other from Roche/Genentech, outside the submitted work.

E.F. Smit: Dr. Smit reports other from Lilly, other from Boehringer Ingelheim, other from Bayer, other from Roche/Genentech, other from AstraZeneca, outside the submitted work.

J.G. Aerts: Dr. Aerts reports other from MSD, other from Boehringer, other from BMS, other from Eli-Lilly, other from Astra-Zeneca, outside the submitted work.

A-M.C. Dingemans: Dr. Dingemans reports other from Roche/Genentech, other from MSD Oncology, other from AstraZeneca, other from Pfizer, other from Lilly, other from Boehringer Ingelheim, other from Bristol-Myers Squibb, other from Clovis Oncology, outside the submitted work.

Author's contribution

J.H.R.J. Degens, K.J.C. Sanders: designed research, conducted research, analyzed data, wrote paper.

E.E.C. de Jong, H.J.M. Groen, E.F.Smit, J.G. Aerts: provided essential material.

A.M.W.J. Schols: designed research, had primary responsibility for final content.

A-M.C. Dingemans: provided essential material, designed research, had primary responsibility for final content.

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