ORIGINAL ARTICLE

Rapid atrophy of cardiac left ventricular mass in patients with non-small cell carcinoma of the lung

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Abstract

Background Cancer is a systemic catabolic condition affecting skeletal muscle and fat. We aimed to determine whether cardiac atrophy occurs in this condition and assess its association with cardiac function, symptoms, and clinical outcomes.
Methods Treatment naïve metastatic non-small cell lung cancer patients (*n* = 50) were assessed prior to and 4 months after commencement of carboplatin-based palliative chemotherapy. Methods included echocardiography for left ventricular mass (LVM) and LV function [LV ejection fraction, global longitudinal strain (GLS), diastolic function], computed tomography to quantify skeletal muscle and total adipose tissue, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), validated questionnaires for dyspnoea and fatigue, plasma biomarkers, tumour response to therapy, and overall survival.
Results During 112 ± 6 days, the median change in LVM was −8.9 [95% confidence interval (95% CI) −10.8 to −4.8, $P < 0.001$]. Quartiles of LVM loss were −20.1%, −12.9%, −4.8%, and +5.5%. Losses of muscle, adipose tissue, and LVM were frequently concurrent; LVM loss > median value was associated with loss of skeletal muscle [odds ratio (OR) = 4.5, 95% CI: 1.4–14.8, P=0.01] and loss of total adipose tissue (OR = 10.0, 95% CI: 2.7–36.7, $P < 0.001$). LVM loss was associated with decreased GLS (OR = 6.6, 95% CI: 1.9–22.7, P=0.003) but not with LV ejection fraction or diastolic function. In the population overall, plasma levels of C-reactive protein (P=0.008), high sensitivity troponin T (hs-TnT) (P=0.03), and galectin-3 (P=0.02) increased over time, while N-terminal pro B-type natriuretic peptide and hs-cTnI did not change over time. C-reactive protein was the only biomarker associated with LVM loss but at the univariate level only. Independent predictors of LVM loss were prior weight loss (adjusted OR = 10.2, 95% CI: 2.2–46.9, P=0.003) and tumour progression (adjusted OR = 14.6, 95% CI: 1.4–153.9, P=0.02). LVM loss was associated with exacerbations of fatigue (OR = 6.6, 95% CI: 1.9–22.7, P=0.003), dyspnoea (OR = 9.3, 95% CI: 2.4–35.8, P<0.001), and deterioration of performance status (OR = 4.8, 95% CI: 1.3–18.3,P=0.02). Patients with concurrent loss of LVM, skeletal muscle, and fat were more likely to deteriorate in all three symptom domains and to have reduced survival (P=0.05).
Conclusions Intense LVM atrophy is associated with non-small cell lung cancer-induced cachexia. Loss of LVM was associated with emerging alterations of GLS, indicating subtle changes in left ventricular function. Longer term studies are needed to assess the full scope of cardiac atrophy and its impact. LVM atrophy arises in conjunction with losses of fat and skeletal muscle and is temporally associated with meaningful declines in performance status, worsening of fatigue, and dyspnoea, as well as poorer tumour response and decreased survival. The specific contribution of LVM atrophy to these outcomes requires further study.

Keywords Cardiac atrophy; Cancer; Cachexia; Left ventricular mass

Introduction

Cancer cachexia is a systemic catabolic condition associated with losses of skeletal muscle and adipose tissue[1]; however, the potential for *cardiac atrophy* is unclear in the clinical context. Studies in rodent models of cancer cachexia suggest that cardiac atrophy may occur. In rodents implanted with tumours, cardiac muscle loss occurs to a similar degree as in skeletal muscles, by pathways involving inflammation, proteolysis, apoptosis, and autophagy.[2] Rodents with cancer also show progressive decline in left ventricular ejection fraction (LVEF) and diastolic function.[2,3] Cardiac atrophy is a little known clinical entity, compared with cardiac hypertrophy, a prevalent pathology associated with hypertension and obesity.[4] Cardiac atrophy occurs in conditions of unloading (e.g. bed rest[5] and use of ventricular assist devices[6]) and in anorexia nervosa.[7] There are a few studies showing cardiac atrophy in cancer patients receiving highly cardiotoxic chemotherapy.[8–10] There have been no prospective longitudinal studies designed to determine whether human cancer cachexia is associated with cardiac atrophy over time.

The rate of atrophy of different muscles (skeletal, respiratory, and cardiac) over the course of cachexia is not well characterized. One possibility is that mobilization of fat reserves and skeletal muscles is prioritized and that muscles involved in vital functions would tend to be spared. Regarding cardiac structural changes in response to weight loss in non-cancer individuals, several publications on weight reduction in obese persons suggest sparing of the cardiac mass [i.e. loss of weight is more pronounced than loss of LV mass (LVM)].[11–13] However, in cachexia, all muscles might atrophy simultaneously, if the tumour-related catabolic drive generates signals acting on the different muscles and other tissues.

Cachexia is associated with progressive impairment of the capacity for physical work and strength, decline in performance status (PS), and increased symptoms such as fatigue and dyspnoea, the latter are already prominent in patients with non-small cell lung cancer (NSCLC). These are important detriments to the quality of life of patients with advanced malignant disease. Skeletal muscle atrophy and reduced dietary intake may in part explain these symptoms. Dietary intake of patients with cachexia is typically insufficient to meet even basal metabolic demands, and fatigue is a well-characterized consequence of chronic malnutrition. Skeletal muscle is implicated in all forms of physical functioning including respiration; muscle loss is a likely driver of dyspnoea, fatigue, and functional impairment. Fatigue, dyspnoea, and reduced physical functioning experienced by cancer patients could be in part associated with cardiac atrophy as these symptoms are well-known consequences of primary cardiac dysfunction.[14,15]

The main aim of this study was to test whether LVM atrophy and changes in cardiac function occur in patients affected by a malignancy with a known propensity for inducing cancer cachexia and metastatic NSCLC.[16] Secondary analyses focused on association between LVM atrophy and symptoms, PS, tumour response to treatment, dose-limiting toxicity, and overall survival.

Materials and methods

Population and study design

This was a longitudinal investigation of LVM (as a measure of heart mass) and cardiac function. The study was approved by the Health Research Ethics Board of Alberta. To limit variability, inclusion was restricted to stage IV NSCLC patients who were eligible for 1st line therapy, for a maximum of four cycles. All patients met eligibility criteria for carboplatin-based doublet therapy ECOG[17] and had PS ≤ 2. Patients with any other active malignancy in the last 5 years were excluded. The number of patients with overt cardiovascular disease was limited by the eligibility criteria for receiving these cancer treatments: that is, adequate renal, hepatic, and haematological function and no stroke or myocardial infarction in the past 3 months. Additional study-specific exclusion criteria were dilated, hypertrophic, or diabetic cardiomyopathy; peripheral vascular disease requiring intervention; and uncontrolled diabetes or hypertension. Study evaluations were conducted before the start of chemotherapy and 2–4 weeks after the last planned (4th) cycle of chemotherapy (~3.5–4 months after enrolment).

Non-small cell lung cancer is one of the cancers strongly associated with cachexia and is the target population for clinical trials of cachexia therapy.[16] However, this is a vulnerable, ill, and rapidly deteriorating group of patients. Because participants may become unable to attend a cardiac imaging facility at follow-up evaluations, we chose echocardiography as the modality of choice to maximize participation, because ultrasound is portable and can be taken to point of care.

Primary outcome: cardiac structure and function

Echocardiography was performed using an Epiq® scanner (Philips Medical Systems, Bothell, WA, USA) according to the 2015 ASE/EACVI Recommendations for Chamber Quantification and 2016 Recommendations for Evaluation of Diastolic Function by Echocardiography[18]. LVEF was calculated using the biplane Simpson method. The 2D-guided M mode was performed to measure LVM according to the guidelines of American Society of Echocardiography.[19]

Two dimensional images from three apical views (four-chamber, two-chamber, and long-axis views) were used for measurement of global longitudinal strain (GLS) using Qlab 10.2 software (Philips). After setting markers on mitral ring and the apex, the software automatically tracks the endocardial borders and places the segments for measurement of regional strain. The average of the peak systolic strain of 16

segments was reported as GLS. Visual assessment of each segment's tracking performance was required. If tracking was suboptimal in certain segments, manually adjusting the endocardial border tracing of these segments was performed.

Left ventricular diastolic function was graded normal, mild (Grade I), moderate (Grade II), and severe (Grade III) depending on the measurements of pulsed-wave Doppler of mitral inflow, tissue Doppler of mitral annulus movement, left atrium volume measurement, and CW-Doppler of the tricuspid regurgitation if present.[18]

Echocardiographic measurements were acquired by two experienced sonographers. For consistency, for the data presented in this paper, all reads were performed by a single, clinical echocardiographer with 33 years' experience (H. B.). Sonographers and echocardiographer were blinded to the results of other assessments. To verify that the findings could be reproduced by another echocardiographer, a second cardiologist performed three reads on 15 randomly selected cases for assessment of the LVM. The mean percentage error between the two cardiologists was 11.4% ± 9.1%

Twelve-lead electrocardiography (ECG) was performed and major parameters including heart rate, PR interval, QRS duration (QRSD), and heart rate corrected QT interval (QTc) were abstracted.

Axial computed tomography images at the 3rd lumbar vertebra were used to assess skeletal muscle and total adipose tissue by validated methods.[20,21] Image parameters included contrast enhanced, 5 mm slice thickness, 120 kVp, and ~290 mA. A single expert in anatomic radiology assessed all images and was blinded to other study findings. Muscles and adipose tissue were quantified within Hounsfield unit ranges of −29 to 150 and −190 to −30, respectively, using Slice-O-Matic software (v.4.3; Tomovision, Montreal, Quebec, Canada).

Secondary outcomes: clinical assessments and functional measures

Performance status was evaluated according to ECOG.[17] Functional Assessment of Chronic Illness Therapy-Fatigue scale was used for fatigue assessment.[22] Medical Research Council (MRC) breathlessness scale[23] was used to score the level of dyspnoea. Dose-limiting toxicity was defined as any chemotherapy adverse effect that results in dose reduction, temporary, or permanent discontinuation of treatment.[24] National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03) was utilized for toxicity assessment. Medication history of patients up to 1 month prior to enrolment and tumour response by RECIST 1.1 criteria[25] were collected.

Plasma biomarkers

Samples for high-sensitivity cardiac troponin T and I (hs-cTnT and hs-cTnI, respectively), galectin-3, and N-terminal pro-B

natriuretic peptide (NT-pro-BNP) were drawn into BD Vacutainer® K2EDTA coated tubes. Samples for C-reactive protein (CRP) were drawn into lithium heparin BD Vacutainer® coated tubes. Samples were stored frozen at −80°C until analysed.

hs-cTnT was measured using an immunoassay analyser (E-modular, Roche Diagnostics). The limits of blank (LoB) and detection (LoD) for hs-cTnT were 3 and 5 ng/L, respectively, and we considered the value of 2.99 ng/L for concentrations below the LoB. The upper reference limit (99th percentile) of the assay is 14 ng/L [95% confidence interval (95% CI): 12.7–24.9]. The lowest stated concentration with a coefficient of variance (CV) ≤ 10% with the hs-TnT assay is 13 ng/L. NT-pro-BNP was also measured by an immunoassay analyser (E-modular, Roche Diagnostics). The LoD of this assay is 5 ng/L with measuring range of 5–35 000 ng/L. hs-cTnI and galectin-3 were measured using chemiluminescent microparticle immunoassays (ARCHITECT i1000; Abbott Diagnostics). The LoB and LoD for hs-cTnI measurement were <1 and 1.2 ng/L. The precision at 99th percentiles of 26.2 ng/L is 4.0%. The lowest concentration with a CV ≤ 10% with the hs-cTnT assay is 4.7 ng/L. For galectin-3, the LoB and LoD of the assay were 1 and 1.1 ng/mL, respectively. The assay has a CV ≤ 10% for measurements ranging from 4.0 to 114.0 ng/mL.

C-reactive protein was measured by enzyme-linked immunosorbent assay (Synchron LX system, Beckman Coulter). Functional sensitivity defined as the lowest concentration that can be measured with CV = 20% is ≤0.18 mg/L.

Statistical analysis

We used SPSS software version 24 (Chicago, IL, USA). Normally and non-normally distributed quantitative variables were tested using analysis of variance and Mann–Whitney U-tests, respectively; χ^2 and bivariate logistic regression were used for categorical variables. For change over time, paired t-test and Wilcoxon tests were used.

The study was planned to detect LVM atrophy as the primary outcome. No human data on cardiac atrophy was available for sample size calculation, so we assumed that effect size and variance might be similar to values reported for skeletal muscle atrophy.[3] Computed tomography-defined skeletal muscle loss in cancer patients on chemotherapy was −4.2% to −6.3% (SD 7.8)[26,27]; we used the lower of these values (−4.2%), α of 0.01 and a power of 90%, yielding a sample size of n = 50 in a paired t-test to detect cardiac atrophy.

Secondary analyses of an exploratory nature were planned to detect potential association of LVM loss with cardiac functions, symptoms, tumour progression, and overall survival. These were studied using univariate and multivariate binary logistic analyses. Kaplan–Meier curves and log–rank tests were utilized for analyses of overall survival, defined as the

number of days from the 1st day of carboplatin-based therapy until death. Data were censored on 1 August 2017.

Results

Baseline patient features are shown (*Table* 1). From October 2013 to May 2016, 91 patients were approached, 72 consented, 70 had baseline measurements, and 50 reached the 2nd time point at a mean of 112 ± 6 days later (see Materials and methods section). The rate of attrition was similar to other lung cancer cachexia trials[16] and entirely expected in the context of 1st line therapy for NSCLC. Three patients were excluded due to a change in treatment plan to cisplatin. A further 17 patients did not complete the 2nd time point: 10 died and 7 patients were bedridden, comatose, or admitted in hospice. Patients who did not complete had significantly higher baseline values of CRP; however, age, sex, PS, tumour histology, and symptoms were not different (*Table* S1). This is consistent with the well-known association of elevated CRP with mortality in advanced stage NSCLC.[28,29]

Included patients were 96% of ECOG-PS 0 (asymptomatic, fully active, and able to carry on all pre-disease activities without restriction) or 1 (symptomatic but completely ambulatory, restricted in physically strenuous activity but ambulatory, and able to carry out work of a light or sedentary nature). These ECOG criteria are rather similar to New York Heart Association (NYHA) scores 1 and 2, respectively. Major cardiac disorders were absent because of exclusion; however, nine patients had mild LV hypertrophy at baseline by ASE criteria (women > 88 g/m^2, men > 102 g/m^2).[30] Included patients had well controlled hypertension (32%) and diabetes (16%) and 10% had a history of myocardial infarction (MI) > 5 years previous to cancer diagnosis. As indicated in *Table* 1, at baseline, 18% were on angiotensin-converting-enzyme inhibitors, 10% on angiotensin receptor blocker and 26% were on beta-blockers, mainly for the management of hypertension; $n = 5$ patients with a prior history of MI were also taking beta-blockers. No patients started new medications of these types during the study. All patients on these agents at baseline continued them throughout chemotherapy, although three patients with hypertension had a dose reduction of their anti-hypertensive therapy during the study.

Left ventricular mass atrophy is associated with non-small cell lung cancer cachexia

Echocardiography-defined LVM fell over time: ($P < 0.001$) (*Table* 2). The percent change of LVM over time was correlated with change of body mass index (BMI) over time (r^2 0.3588, P=0.01) (*Figure* S1). The median overall change in LVM was -8.9% (95% CI: -10.8 to -4.8, $P < 0.001$). LVM loss distribution is illustrated by quartiles: Q1, -20.1%; Q2, -12.9%; Q3, -4.8%; Q4, $+5.5\%$ (*Figure* 1D); maximum LVM

Table 1 Baseline characteristics of patients with metastatic NSCLC (*N* = 50)

Demographic data	Age (years)	64.8 ± 7.8
	Male, *n* (%)	24 (48)
	Caucasian, *n* (%)	49 (98)
Tumour histology	Adenocarcinoma	36 (72)
	Squamous cell carcinoma	11 (22)
	Others	3 (6)
Chemotherapy added to carboplatin	Vinorelbine, *n* (%)	15 (30)
	Gemcitabine, *n* (%)	8 (16)
	Paclitaxel, *n* (%)	1 (2)
	Pemetrexed, *n* (%)	26 (52)
Prior chest radiotherapy		23 (46)
Biochemical parameters	White blood cell (×10^9/L)	8.3 ± 3.9
	Haemoglobin (g/L)	129.7 ± 15.8
	Platelet (g/L)	329.7 ± 107.1
	Creatinine (μmol/L)	73.9 ± 24.7
	Na (mmol/L)	139.8 ± 3.5
	K (mmol/L)	4.5 ± 0.4
Cardiovascular risk factors	Hypertension, *n* (%)	16 (32)
	Diabetes mellitus, *n* (%)	8 (16)
	Smoking, *n* (%)	41 (82)
	Prior myocardial infarction, *n* (%)[a]	5 (10)
Drug history one month before start of chemotherapy	ACE inhibitor, *n* (%)	9 (18)
	Angiotensin receptor blocker, *n* (%)	5 (10)
	Beta-blocker, *n* (%)	13 (26)
	Statin, *n* (%)	14 (28)
Weight loss history	>5% weight loss in recent 6 months, *n* (%)	21 (42)

Values are expressed as mean ± SD. ACE, angiotensin converting enzyme; NSCLC, non-small cell lung cancer.
[a]Recent myocardial infarction (3 month before inclusion) was an exclusion criterion.

Table 2 Body composition, cardiac parameters, and functional indices at baseline and at study endpoint (*n* = 50)

		Time course		
		Baseline; Day 0	Post-treatment; Day 112 ± 6	*P* value
Weight and body composition	Body mass index (kg/m^2)	26.5 ± 5.8	25.5 ± 5.4	0.001
	Skeletal muscle (cm^2)	130.5 ± 36.0	120.9 ± 29.7	<0.001
	Muscle radiation attenuation (HU)	29.4 ± 8.7	27.7 ± 8.5	0.03
	Total adipose tissue (cm^2)	317.9 ± 204.2	290.6 ± 180.5	0.02
Blood pressure	Systolic (mmHg)	124.4 ± 18.2	125.4 ± 19.4	0.61
	Diastolic (mmHg)	74.17 ± 9.5	72.4 ± 10.5	0.18
Echocardiography parameters	LVM (g)	161.9 ± 53.3	148.3 ± 49.6	<0.001
	LVM/body surface area (g/m^2)	86.9 ± 22.6	80.3 ± 20.8	<0.001
	LV posterior wall thickness-diastole (cm)	0.96 ± 0.17	0.89 ± 0.16	0.01
	Inter-ventricular septum-diastole (cm)	1.1 ± 0.18	0.92 ± 0.16	0.003
	LV ejection fraction (%)	58.2 ± 8.0	56.8 ± 7.5	0.006
	Global longitudinal strain (%)	18.6 ± 3.1	17.3 ± 3.6	0.001
	Normal diastolic function, *n* (%)	38 (76)	36 (72)	0.20
ECG parameters	Heart rate (b.p.m.)	78.9 ± 14.9	80.5 ± 15.2	0.39
	PR (ms)	166.6 ± 25.8	195.6 ± 134.5	0.12
	QRS duration (ms)	94.4 ± 19.3	96.2 ± 22.7	0.21
	QTc (ms)	443.7 ± 26.6	448.7 ± 29.4	0.05
Plasma biomarkers[#]	CRP (mg/L)	7.9 (3.4; 22.7)	12.3 (3.9; 35.1)	0.008
	hs-cTroponin T (ng/L)	6.1 (3.8; 12.5)	7.6 (4.9; 15.4)	0.03
	hs-cTroponin I (ng/L)	1.5 (0.6; 3.0)	2.0 (0.1; 4.0)	0.86
	NT pro-BNP (ng/L)	123.5 (60.0; 292.6)	145.5 (71; 433.0)	0.44
	Galectin-3 (ng/mL)	17.7 ± 7.3	19.9 ± 7.0	0.03
Performance status, fatigue, and dyspnoea	FACIT-F fatigue score [0 (worst)–52]	32.4 ± 11.1	28.4 ± 12.6	0.001
	ECOG (0–1), *n* (%) [0–5 (worst)]	48 (96)	20 (40)	<0.001
	MRC-dyspnoea score (1–2), *n* (%) [1–5 (worst)]	44 (88)	20 (40)	<0.001

Values are expressed as mean ± SD or median (interquartile ranges). CRP, C-reactive protein; ECG, electrocardiogram; ECOG, Eastern Co-operative Oncology Group; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; GLS, global longitudinal strain; HU, Houns-field unit; LVM, left ventricular mass; MRC, Medical Research Council; hs-cTroponin T, high sensitivity cardiac troponin T; hs-cTroponin I, high sensitivity cardiac troponin I; NT pro-BNP, N-terminal pro-B natriuretic peptide; LV, left ventricular.

Figure 1 Loss of individual tissues, by quartiles (Q). Variation in tissue loss over time for (A) skeletal muscle, (B) total adipose tissue, (C) body mass index, and (D) left ventricular mass (LVM). In panel (E) variation of cardiac global longitudinal strain (GLS) is shown for each quartile of LVM loss. Patients in Q1 (largest LVM loss) had significantly higher GLS loss (*P* < 0.001).
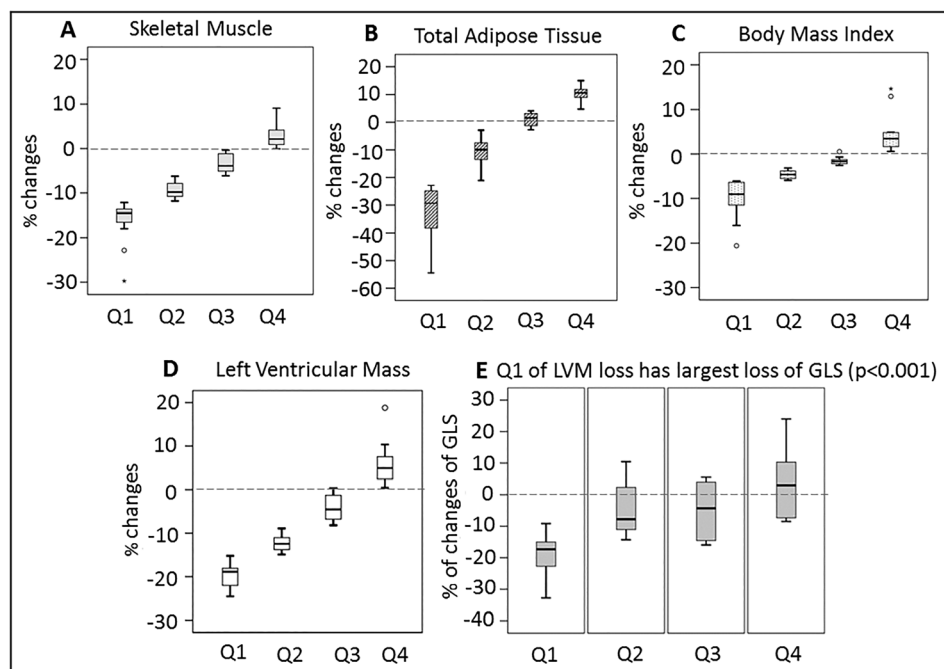
loss was −24.5%. In *Table S2*, the baseline characteristics of patients in the four quartiles of LVM loss are shown. The only baseline characteristic predictive of LVM loss was prior history of weight loss (P=0.002). This is consistent with the progressive nature of cancer cachexia. LVM loss was of similar magnitude in men (−8.5 ± 10.6%) and women (−7.2 ± 10.1%) (P=0.71). LVM indexed to body surface area fell by 7.6% ($P < 0.001$) (*Table* 2). The median overall change in LVM (−8.9%) exceeded that of skeletal muscle (−6.2%) and of adipose tissue (−4.8%). Quartiles of muscle, fat, and BMI loss are illustrated in *Figure* 1A–C, also showing distinctive behaviour ranging from stable to severe loss. This is consistent with the well-known inter-individual variation in the presence or absence and severity of cachexia in patients with NSCLC.[31]

Loss of LVM, skeletal muscle, and fat were frequently concurrent within individual patients. Patients whose LVM loss was ≥ median value were at a higher risk of loss ≥ the median value for skeletal muscle [odds ratio (OR) = 4.5, 95% CI: 1.4–14.8, P=0.01] and of total adipose tissue loss (OR = 10.0, 95% CI: 2.7–36.7, $P < 0.001$) (*Table* 3A). A Venn diagram (*Figure* 2A) illustrates the considerable overlap of LVM, skeletal muscle, and adipose tissue loss: 17 of 25 patients with LVM loss ≥ the median value, concurrently lost skeletal muscle and 19 of 25 concurrently lost total adipose tissue. A small number of patients had isolated fat loss (n = 6) or isolated skeletal muscle loss (n = 8). No patients showed isolated LVM loss; this was always associated with muscle and/or fat loss; 11 of 50 patients had concurrent loss of LVM, skeletal muscle, and adipose tissue (*Figure* 2A).

Cardiac function and biomarkers

The major cardiac functional change was a decline in GLS, by a median of 8.1% (interquartile range: 15.0; 4.1, P<0.001), and this was especially prominent in patients in the largest quartile of LVM loss ($P < 0.001$) (*Figure* 1E). There was no change in the proportion of patients with normal diastolic function over time (76% vs. 72%; P=0.20) (*Table* 2). There was a small overall decline of LVEF (58.2 ± 8.0% to 56.8 ± 7.5%; P=0.006) and a small increase in QTc (443.7 ± 26.6 to 448.7 ± 29.4 ms; P=0.05). Plasma levels of the cardiac biomarkers hs-cTnT (P=0.03) and galectin-3 (P=0.02) were increased, while NT-pro BNP and hs-cTnI did not change over time (*Table* 2). None of the cardiac biomarkers was associated with LVM loss.

Left ventricular mass loss ≥ median was associated with decline of GLS (OR = 6.6, 95% CI: 1.9–22.7, P=0.003) (*Table* 3C) and with decreased QRSD (OR = 4.5, 95% CI: 1.4–14.8, P=0.01); however, LVM loss ≥ the median value was not significantly related to loss of LVEF or other ECG parameters.

Secondary analyses

Potential predictors of LVM loss were evaluated (*Table* 4). In this analysis, we considered factors that have been suggested in the literature to reflect increased catabolic drive in tumour-bearing state, inflammation, ongoing weight loss, progressive disease in spite of anticancer therapy, and cancer treatments. Prior chest radiotherapy did not associate with development

Table 3 Univariate association between LVM loss and other clinical features over time

	Clinical features stable vs. deteriorating	Patients with LVM loss >8.9%, N (%)	Unadjusted odds ratio	P value
A. Skeletal muscle and fat	Skeletal muscle loss[a] (n = 25)	17 (68)	4.5 (1.4–14.8)	0.01
	Skeletal muscle stable (n = 25)	8 (32)		
	Total adipose tissue loss[b] (n = 25)	19 (76)	10.0 (2.7–36.7)	<0.001
	Total adipose tissue stable (n = 25)	6 (24)		
B. Performance status, fatigue, and dyspnoea	Fatigue worsening[c] (n = 25)	18 (72)	6.6 (1.9–22.7)	0.003
	Fatigue stable (n = 25)	7 (28)		
	Dyspnoea worsening[d] (n = 30)	21 (70)	9.3 (2.4–35.8)	0.001
	Stable dyspnoea (n = 20)	4 (25)		
	PS worsening[e] (n = 16)	12 (75)	4.8 (1.3–18.3)	0.02
	Stable PS (n = 34)	13 (38.2)		
C. Cardiac functional parameters	Global longitudinal strain loss[f] (n = 25)	18 (72)	6.6 (1.9–22.7)	0.003
	Global longitudinal strain stable (n = 25)	7 (28)		
	Left ventricular ejection fraction loss[g] (n = 25)	12 (48)	0.85 (0.3–2.5)	0.78
	Left ventricular ejection fraction stable (n = 25)	13 (52)		
	Impaired diastolic function[h] (N = 14)	8 (57.1)	1.5 (0.43–5.2)	0.53
	Normal diastolic function (N = 36)	17 (47.2)		

LVM, left ventricular mass; PS, performance status.
[a]Computed tomography-defined skeletal muscle loss > median overall value (−6.2%).
[b]Computed tomography-defined total adipose tissue (fat) loss > median overall value (−4.6%).
[c]Loss of Functional Assessment of Chronic Illness Therapy-Fatigue-defined score > median value (−12.5%).
[d]Patients whose dyspnoea scores increased over time and were within the clinically meaningful worsened status (Medical Research Council ≥ 3).
[e]Patients whose PS increased over time and reached the clinically meaningful worsened PS (Eastern Cooperative Oncology Group ≥ 3).
[f]Global longitudinal strain loss > median overall value (−8.1%).
[g]Left ventricular ejection fraction loss > median overall value (−2%).
[h]Impaired (Grade I, II, or III) or normal diastolic function at follow up.

Figure 2 Concurrent tissue losses. (A) Association between loss of left ventricular mass (LVM), skeletal muscle and fat (total adipose tissue). A Venn diagram illustrates the overlap of patients with tissue loss > median overall values for each tissue. *N* = 11 (22%) patients showed no tissue loss (dotted circle). Other patients lost one tissue (muscle or fat), two tissues (LVM with either muscle or fat), or all three tissues. No patients showed isolated LVM loss; this was always associated with muscle and/or fat loss. (B1–B4) Association between tumour response to therapy and number of tissues lost (*P* < 0.001): (B1) 64% partial response, 36% stable disease; (B2) 50% partial response, 50% stable disease; (B3) 14% partial response, 50% stable disease, 36% progressive disease; and (B4) 36% stable disease, 64% progressive disease. (C1–C4) Association between number of tissue lost and exacerbation of fatigue, dyspnoea, and performance status. During the study, individual patients experienced exacerbation in none, one, any two, or all three of performance status (ECOG-PS), dyspnoea (MRC), and fatigue (FACIT-F). The greater the number of tissue losses, the greater the number of symptoms were experienced (C1–C4) (P=0.02). (C1) Of the patients who did not show any loss of muscle, fat, or LVM, 64% did not experience any symptoms and the remaining 36% had a single symptom worsen over the course of the study. (C4) At the distal end of this spectrum, 64% of patients with three tissues loss experienced clinically important worsening of all three symptoms (fatigue, dyspnoea, and performance status). (D) Survival by number of tissues lost. Kaplan–Meier curves and log–rank analysis were considered to detect the differences between groups of patients. (D1) Survival by number of tissues lost. There were no differences between groups with zero and one tissue losses; likewise, the survival of patients who lost any two or three tissues was similar. (D2) Log–rank test was used to compare survival between two groups of patients (0 or 1 tissue loss vs. 2 or 3 tissue loss; P=0.05).
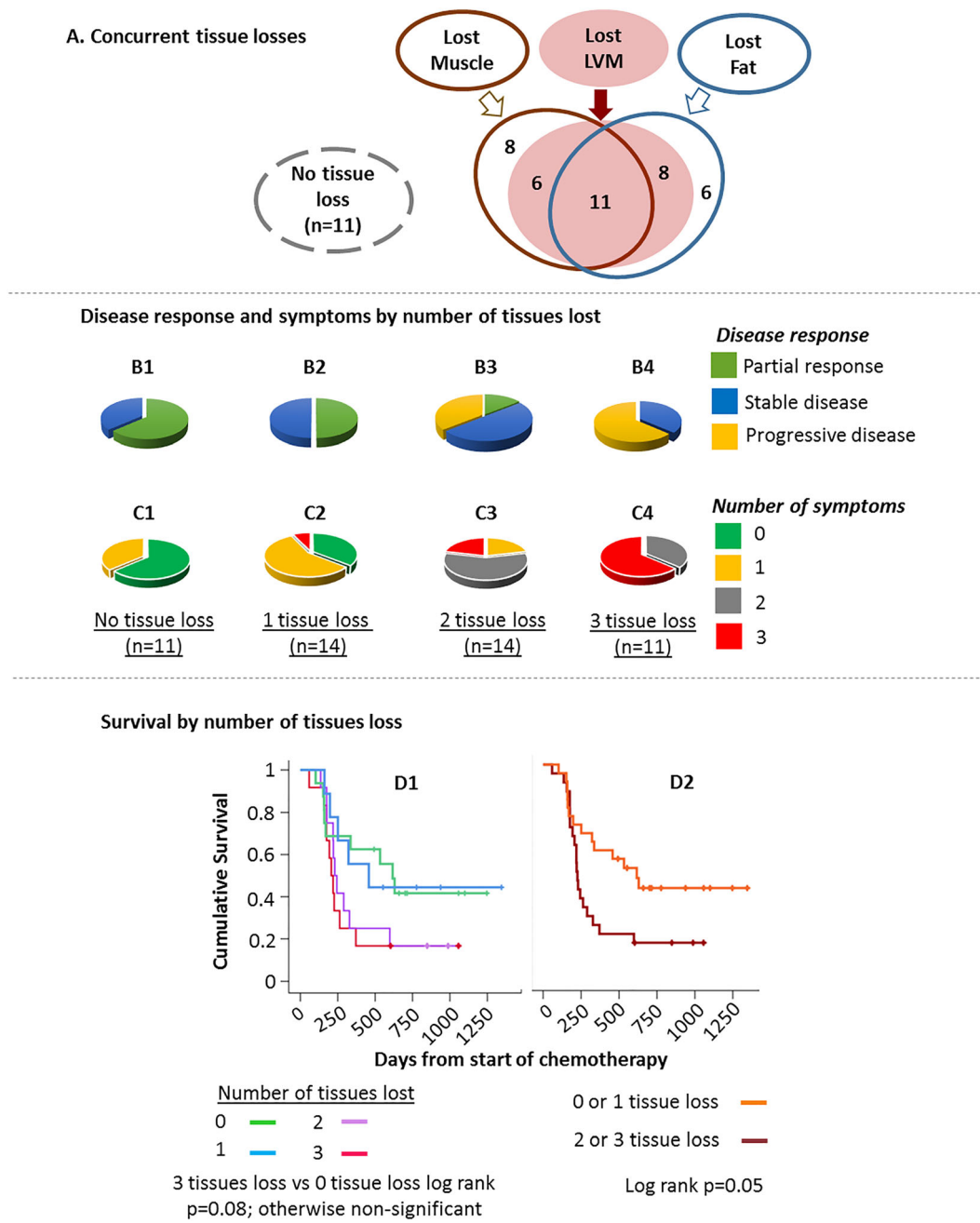
Table 4 Predictive factors for development of LVM loss over time

Univariate analysis	LVM loss >8.9%, N (%)	Unadjusted odds ratio (95% CI)	P value
Progressive disease (N = 12)	11 (91.6)	18.8 (2.2–162.0)	0.007
Stable disease or partial response (n = 38)	14 (36.8)		
>5% weight loss[a] (n = 21)	17 (81.0)	11.2 (2.9–43.5)	<0.001
<5% weight loss (n = 29)	8 (27.5)		
Baseline CRP > 10 (mg/L) (n = 22)	15 (68.2)	3.9 (1.2–12.6)	0.02
Baseline CRP < 10 (mg/L) (n = 28)	10 (35.7)		
Pemetrexed (n = 26)	12 (46.2)	0.72 (0.24–2.2)	0.57
Other agents (n = 24)	13 (54.2)		
Prior chest radiotherapy (n = 23)	12 (52.2)	1.17 (0.39–3.6)	0.78
No chest radiotherapy (n = 27)	13 (48.1)		

Multivariate analysis	LVM loss > 8.9% N (%)	Adjusted odds ratio (95% CI)	P value
Progressive disease (N = 12)	11 (91.6)	14.6 (1.4–153.9)	0.02
Stable disease or partial response (n = 38)	14 (36.8)		
>5% weight loss (n = 21)	17 (81.0)	10.2 (2.2–46.9)	0.003
<5% weight loss (n = 29)	8 (27.5)		
Baseline CRP > 10 (mg/L) (n = 22)	15 (68.2)	2.4 (0.5–10.9)	0.2
Baseline CRP < 10 (mg/L) (n = 28)	10 (35.7)		

CRP, C-reactive protein; LVM, left ventricular mass.
[a]Weight loss >5% in 6 months preceding chemotherapy.

of LVM loss over time. Eligibility for participation was restricted to carboplatin-based regimens, but this treatment plan allows for a variety in the 2nd agent used in the carboplatin-doublet therapy; this also not associated with LVM loss. By contrast, CRP > 10 mg/L, weight loss >5% in the months prior to baseline, and progressive disease (vs. stable disease/partial response) were associated significantly with LVM loss. In multivariate analyses, progressive disease (adjusted OR = 14.6, 95% CI: 1.4−153.9, P=0.02) and prior weight loss (adjusted OR = 10.2, 95% CI: 2.2–46.9, P=0.003) were associated with LVM loss (*Table* 4). Characteristics not associated with LVM loss included age, sex, cardiac systolic and diastolic function, hypertension, diabetes, prior MI, baseline use of angiotensin-converting-enzyme inhibitors, or angiotensin II receptor blockers (data not shown). We also conducted a univariable/multivariable linear regression analysis of possible associations between LVM loss over time and changes in other clinical variables over time (*Table* S3). At the univariate level, loss of LVM was correlated ($P < 0.001$) with loss of BMI ($r = 0.56$), loss of total fat ($r = 0.52$), reduction in GLS ($r = 0.65$), decline in ECOG-PS ($r = 0.53$), development of fatigue ($r = 0.51$), and dyspnoea ($r = 0.46$). Loss of LVM and of skeletal muscle were not strongly related ($r = 0.3, 0.1$). Independent associations were confirmed between fat loss, decline of GLS, and ECOG-PS, with loss of LVM over time.

Association of LVM loss with PS, fatigue, and dyspnoea was also evaluated. Overall, patients experienced deterioration of ECOG-PS ($P < 0.001$), exacerbation of fatigue (P<0.001) and Medical Research Council dyspnoea score ($P < 0.001$) (*Table* 2). In univariate analysis, development of poor PS, severe dyspnoea, and fatigue associated with LVM atrophy over time (*Table* 3B). Quantifying the specific contribution of cardiac atrophy to patients' burden of symptoms is difficult because of simultaneous muscle and/or fat loss (*Figure* 2A). The greater

the number of concurrent tissue losses, the more likely that a patient would experience deterioration of PS and symptoms (P=0.02; *Figure* 2C1–C4).

Disease and treatment outcomes in relation to left ventricular mass loss

Tumour response to chemotherapy was less likely in patients who lost multiple tissues concurrently (i.e. individuals in the centre of the Venn diagram) as compared with patients with limited or no tissue loss ($P < 0.001$; *Figure* 2B1–B4). The same patients were at higher risk of mortality (P=0.05; *Figure* 2D2). Disease progression also differed between groups of patients with LVM loss vs. patients with stable LVM over time ($P < 0.001$): 12/25 (48%) progressive disease; 3 (12%) partial response and 10 (40%) stable disease vs. 0/25 (0%) progressive disease; and 13 (52%) partial response and 12 (48%) stable disease. Median (interquartiles) of overall survival of patients with LVM loss vs. patients with stable LVM were 226 (208–244) days and 513 (118–948) days, respectively; however, it did not reach significance (0.10) (*Figure* S2).

During treatment, patients with LVM loss were more likely to experience dose-limiting toxicity from their carboplatin-based palliative chemotherapy (univariate OR = 6.5, 95% CI: 1.2–34.0, P=0.03).

Discussion

Cardiac atrophy in non-small cell lung cancer

Rapid cardiac atrophy occurs in patients with metastatic NSCLC. Individual patients appeared on a spectrum ranging

from no loss of LVM to a maximum loss of 24.5% in a period of just 112 days. Currently, the median life span of metastatic NSCLC patients is ~15 months. Given that our observations were taken over ~3.7 months, we possibly witnessed only a small part of the total LVM loss. It seems plausible that our patients had experienced some cardiac atrophy prior to our baseline, because many had weight loss during the 6 months preceding study participation. Given that prior weight loss was a strong predictor of cardiac atrophy, further losses of LVM were likely to have occurred during disease progression subsequent to our observation period, as catabolic losses of skeletal muscle and fat accelerate during 12 months preceding cancer death.[26,32] A longer term study would be required to fully evaluate cardiac atrophy and its clinical impact across the patient journey. An international consensus characterizes cancer cachexia as '… loss of skeletal muscle mass with or without loss of adipose tissue … associated with progressive functional impairment'[33]; however, cardiac mass is not spared, and indeed, the higher rate of LVM loss as compared with other tissues resulted in a disproportionally lower ratio of LVM to body surface area by end of study.

We did not have access to a non-cancer control group in our study; however, it is possible to compare our findings of pronounced cardiac atrophy with the literature. In some studies of patients with cancer on chemotherapy, a healthy control group was included,[9] and over 6 months, the healthy controls showed no change in LVM or functional cardiac parameters. This is not surprising, as in older community-dwelling people, LVM is often stable over many years[34] (a longitudinal study over 4 years and 16 years). Of perhaps greater interest is comparing our findings with studies of weight loss in healthy persons. In several studies in patients subjected to medical or nutritional interventions to induce weight loss, a decline in LVM was absent or much less pronounced than the fall in BMI. For example, in obese patients on a 12 week intervention (diet restriction to 800 kcal/day), a similar time frame to our study, patients lost 7.1 kg/m^2 (19% of body weight) without any detectable change in LVM.[11] In two studies over 6 months post-bariatric surgery, weight loss was very large (~ −13 kg/m^2); however, the loss of LVM per 1 unit loss of BMI was −0.53%[12] and −0.61%.[13] These changes are very modest compared with our NSCLC patients (LVM loss per unit BMI loss −3.5%; overall LVM loss −8.9%).

The main functional change in the heart was reduced GLS. GLS is useful in early detection of subclinical LV dysfunction, and in some conditions, a large fall in GLS may be a prelude to decreased LVEF in cancer patients.[35,36] GLS in combination with LVEF is recommended to monitor patients undergoing chemotherapy with potential cardiotoxic drugs.[37] The main index of systolic function, LVEF, was slightly lower at the 2nd study time point, and diastolic function was not altered. These results are consistent with rodent studies in which at least 20% loss of LVM

was required,[3] before significant impairments occurred in LVEF and diastolic parameters.[3] In isolated working hearts from a cancer cachexia rat model, 10% cardiac mass loss is associated with impairment of contractile function, while pumping performance remained intact[38]; this is concordant with our finding that 8.9% LVM loss was associated with GLS impairment with preserved LVEF. We did observe two sub-clinical and possibly early changes associated with LVM atrophy, decreased ECG-defined QRSD, and echocardiography-defined GLS. There are some data to suggest a positive relation between increased QRSD and LVM.[39]

It will be difficult to completely differentiate to what extent the cardiac changes we saw were due to cancer and cachexia and in what extent they might have been due to cardiotoxicity. Changes in LVM were associated strongly with muscle and fat loss (cachexia association) and also more prominent in patients with progressive disease (cancer association). However, there is a literature on cardiotoxic chemotherapy to draw on, especially anthracyclines, which are among the most prominent of the cardiotoxic agents. Anthracyclines cause clinically important reduction in LVEF and cardiac atrophy.[8–10] We tried to choose a treatment regimen with minimal cardiotoxicity (carboplatin-based); however, there is always a possibility of some cardiotoxicity. All patients in our sample received the same carboplatin dose; however, while there was variation in the second agent (gemcitabine, pemetrexed, vinorelbine, or paclitaxel) neither loss of LVM not decline in GLS associated with these different agents (P=0.7) (data not shown). The 2016 European Society of Cardiology position paper[40] on cancer treatment and cardiovascular toxicity does not list carboplatin as a cause of LV dysfunction. This statement depends on a definition based on reduced LVEF and does not consider any sub-clinical[41] or biomarker-based criteria.[42] None of our patients showed cardiotoxicity as conventionally understood (i.e. a 10% decrease in LVEF). The subtle deterioration of LV function (GLS-defined) might be interpreted as signs of cardiotoxicity. In our study, patients with cachexia showed a drop in GLS, and also, Figure 1E shows that patients in Q1 of LVM loss had the largest rate of GLS loss.

While changes in the echocardiography-defined cardiac functions were subtle, PS and the symptoms of fatigue and dyspnoea associated with cachexia and LVM loss showed prominent exacerbation over time. Our data suggest that concurrent losses of LVM, muscle, and fat associate with concurrent development of fatigue, dyspnoea, and reduced PS. These are important detriments to the quality of life of patients with advanced cancer. As we suggest earlier, these problems may be driven in part by emergent cardiac abnormalities, but other dimensions of cachexia may play a role, including worsening inflammation, skeletal muscle atrophy, and negative energy balance. In the continued search for clinical benefit readouts of cachexia therapy, this symptom cluster

could be considered as components of potential composite functional endpoints for future clinical studies.

Mechanisms of cardiac atrophy

Mechanisms involved in cardiac atrophy in NSCLC remain to be fully elucidated. Our results suggest that it is tumour-driven, because its two independent predictors were a prior history of weight loss and lack of tumour response to therapy (progressive disease). In part, cardiac atrophy may be secondary to overall weight loss that would result in reduced cardiac loading conditions (e.g. VO_2, fluid volume) and reduced LV workload. As discussed earlier, weight loss-related loss of LVM has been studied in obese patients;[11,43] however, these are of low small a magnitude compared with our observations (LVM −8.9%; LVM index −7.6%). The majority of patients were smokers, and it is likely that patients had subclinical coronary artery disease. Worsening of coronary heart disease may be associated with deterioration of LV function. However, this typically takes a longer time period and usually results in regional LV wall motion abnormalities that we have seen only in two patients over time. Except in patients post-ST-elevation myocardial infarction, a reduction in LV wall thickness is uncommon in patients with coronary artery disease. Progressing coronary artery disease cannot be excluded, but it is unlikely that the echocardiographic changes during follow up are caused by it. Likewise, changes in blood pressure were minimal and seem unlikely to be important in driving the cardiac changes.

Depletion of either skeletal muscle[21,44,45] or adipose[46] tissue correlate with prognosis in cancer patients. Survival analysis in this study requires confirmation in a larger sample; however, we note with interest that the isolated loss of either fat or muscle was not associated with increased mortality. Rather, concurrent loss of at least two tissues (either muscle or fat, and heart) associated with shortened survival. This might suggest that cardiac atrophy is a late phenomenon, occurring only when muscle and fat loss are already entrenched.

Low skeletal muscle mass has been associated with dose-limiting toxicity (i.e. dose reduction or discontinuation).[21,45,47,48] Alterations in pharmacokinetics of the chemotherapy agent in patients with skeletal muscle depletion are one proposed mechanism connecting cachexia and dose-limiting toxicity. Interaction between cardiac atrophy and cardiotoxic agents (e.g. anthracyclines) may be worthy of investigation, in cancers where cardiotoxic chemotherapies are frequently used.

The literature on mechanisms of cardiac atrophy in rodent models of cancer cachexia is informative; however, one should caution extrapolation of these findings to humans. Detailed studies of morphological, cellular, and biochemical aspects of cardiac atrophy would require heart biopsy, which was out of the scope of our current investigation. In rodents, hyper-inflammation in cancer up-regulates nuclear factor κ-light-chain-enhancer of activated B cells (NFκB) leading to activation of ubiquitin ligases [muscle RING-finger protein-1 (MuRF-1) and atrogin-1/MAFb], which finally forms ubiquitin proteasome system-related catabolism.[2,49] Dysregulation of protein kinase B and subsequent impairment in mammalian target of rapamycin regulatory actions contribute to reduction in anabolic pathways.[3,49]

We focused on inflammatory and cardiac biomarkers. Troponin I and T (cardiomyocyte injury) and BNP (cardiomyocyte stress) have long been studied in heart failure.[50] In some rodent models of cancer cachexia, increased plasma cTn-T[3] and gene expression of BNP in heart tissue[51] have been observed. Here, cardiac specific biomarker (hs-cTnT) increased over time and was associated with concurrent loss of LVM, skeletal muscle, and fat. Galectin-3 also increased but was not related to LVM loss. Circulating galecin-3 has been related to either heart failure[52] or cancer progression.[53]

Methodological considerations and limitations

This was one of few longitudinal studies in a defined cachexia-prone patient population with assessment of muscle and fat loss with high precision imaging and patient-reported outcomes and biomarkers. The selected population is at risk for cachexia, and we reduced heterogeneity by restriction of the stage of disease and treatment plan. Further studies of this design would be useful in the evaluation of the putative cachexia mechanisms and mediators and biomarkers emerging from experimental studies of lung cancer cachexia, such as PTHrP, HSP 70/90, GDF15, interleukin-6, and TWEAK.[1] Our study was appropriately powered for its primary outcome; however, other analyses must be considered exploratory until larger cohorts can be studied.

In future studies, cardiac imaging modalities such as gated cardiac magnetic resonance imaging (MRI) will be required to assess functional and structural changes in the architecture of the heart in more detail. Cardiac MRI would be a more precise tool for these measures; however, we opted for echocardiography to make the study more accessible to patients with advanced NSCLC. Compared with cardiac MRI, echocardiography is more operator-dependent for determination of LVM but is clinically practical and has a minimal burden. Several studies have shown good correlations between cardiac MRI and echocardiography.[54,55] A recent study showed strong correlations and agreement for both modalities and image quality in 146 patients when the same reader assesses the recordings.[54] Because of the availability of experienced sonographers and reading cardiologist, we were confident to detect changes between baseline and follow up.

The generalizability of our results must be further evaluated in other cachexia-prone malignancies and across the cancer trajectory. One of the main points that can be addressed in future studies is considering the association between changes of LVM and changes of skeletal muscle strength[56] and cardiorespiratory fitness (e.g. peak oxygen uptake).[57,58]

Conclusions

Left ventricular mass atrophy arises in conjunction with losses of fat and skeletal muscle in a patient population suffering meaningful declines in PS, worsening of fatigue, and dyspnoea, as well as poorer tumour response, elevated incidence of dose-limiting toxicity, and decreased survival. New cachexia-directed therapeutics with activity towards cardiac atrophy in addition to skeletal muscle and fat loss may be helpful in alleviating the functional impairment and symptoms associated with cancer cachexia.

Acknowledgements

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Correlation between loss of BMI and loss of LVM. This graph shows the relationship between loss of BMI (units are kg/m^2) on the horizontal axis and percentage loss of LVM on the vertical axis in our data on n = 50 NSCLC patients.

Figure S2. Kaplan-Meier curve, comparison between patients with LVM loss versus patients with stable LVM over time. Kaplan-Meier curves and log-rank analysis were used to evaluate the two groups of patients. Median (interquartiles) of overall survival of patients with LVM loss were 226 (208-244) (black line) days versus patients with stable LVM which were 513 (118-948) days (gray line) respectively; however it did not reach significance (P=0.10).

Table S1: Comparison of baseline characteristics of patients who completed study participation versus those who did not reach the second time point

Table S2: Baseline characteristics of patients within different quartiles of LVM change over time

Table S3: Univariable and multivariable linear regression of clinical variables over time versus LVM loss over time

Conflict of interest

All authors declare that they have no conflict of interest.

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