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Changes in muscle measures during chemoradiotherapy in patients with limited stage small cell lung cancer

Christine Damgaard ValanMD, PhD[1,2], Tarje Onsøien HalvorsenMD, PhD[1,2*], Marit SlaaenMD, PhD[3,4] & Bjørn Henning GrønbergMD, PhD[1,2]

[1]*Department of Clinical and Molecular Medicine, NTNU, Norwegian University of Science and Technology, Trondheim, Norway,* [2]*The Cancer Clinic, St. Olav's Hospital, Trondheim University Hospital, Trondheim, Norway,* [3]*Department of Internal Medicine, Innlandet Hospital Trust, Hamar, Norway,* [4]*Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway*

Abstract

Background Concurrent chemoradiotherapy is the recommended treatment for limited stage small cell lung cancer. Severe side-effects, which might cause loss of muscle mass, are frequent. Low skeletal muscle index (SMI) and radiodensity (SMD) are associated with inferior survival and more toxicity in cancer patients, but few have investigated this in small cell lung cancer, and none have investigated whether these muscle measures change during chemoradiotherapy. Patients from a trial comparing two schedules of thoracic radiotherapy (TRT) were analysed (n = 157). We investigated if SMI and SMD changed during treatment; whether changes are negative prognostic factors; or associated with severe toxicity.

Methods Skeletal muscle index and SMD were assessed from computerized tomography scans taken before and after chemoradiotherapy. Patients with analysable computerized tomography scans who completed TRT were eligible.

Results Sixty-eight patients (43.3%) were analysed. Median age was 63 (range 40–85), 16% had performance status 2 and 92% stage III. Mean SMI decreased from 46.25 to 42.13 cm^2/m^2 and mean SMD from 38.40 to 37.46 Hounsfield units. Loss of SMD was significantly associated with less Grades 3–4 toxicity (P = 0.027) and less Grades 3–4 esophagitis (P = 0.029). Loss of SMI was significantly associated with shorter survival in multivariable (P = 0.037) but not in univariable analysis (P = 0.094). Loss of SMD was significantly associated with better survival in both univariable (P = 0.006) and multivariable analyses (P = 0.013).

Conclusions There were large individual variations in changes in muscle measures during chemoradiotherapy, but the majority experienced a loss of both SMI and SMD. There was no consistent prognostic value of changes in muscle measures or consistent associations with severe treatment toxicity.

Keywords Prognostic factor; Predictive factor; Survival; Skeletal muscle index; Skeletal muscle radiodensity

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**Correspondence to: Tarje Halvorsen, Department of Clinical and Molecular Medicine, NTNU, Norwegian University of Science and Technology, Trondheim, Norway, Phone: +47-95-135362. Email:* tarje.halvorsen@gmail.com

Introduction

Loss of skeletal muscle mass and muscle quality in terms of muscle depletion and low radiodensity is linked to cancer cachexia[1] and is associated with poor prognosis and more treatment toxicity from systemic therapy in cancer patients.[2–5] Both can be assessed from computerized tomography (CT) slides and is usually expressed as skeletal muscle index (SMI) and skeletal muscle radiodensity (SMD).[6–8]

Several studies of the clinical role of muscle measures, including studies of lung cancer patients, have been performed, but most have only measured SMI and SMD at baseline. In a

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previous study of advanced non-small cell lung cancer (NSCLC) patients who received palliative chemotherapy, we demonstrated that SMI may change during the treatment period, that gain in SMI was associated with a good response to chemotherapy, and that loss of SMI was a stronger negative prognostic factor than the baseline SMI.[9] There is little data on whether SMD changes during cancer therapy, whether changes in SMI or SMD are associated with severe treatment toxicity, or whether changes in SMD is associated with survival.

Standard treatment for patients with limited stage (LS) small cell lung cancer (SCLC) is concurrent platinum-etoposide chemotherapy and thoracic radiotherapy (TRT). The chemotherapy often causes nausea, anorexia, and neutropenic infections, and the TRT often causes esophagitis, which leads to dysphagia. Both might cause involuntary weight loss and consequently loss of muscle mass. Few have, however, investigated the clinical role of SMI or SMD in SCLC, and none have investigated whether lung cancer patients who undergo potentially curative chemoradiotherapy experience loss of SMI or SMD.

We analysed patients enrolled in a randomized phase II trial comparing two schedules of TRT in LS SCLC.[10] The aims were to investigate to what extent SMI and SMD change from baseline until end of chemoradiotherapy, whether loss of SMI or SMD during chemoradiotherapy are negative prognostic factors or associated with severe treatment toxicity.

Materials and methods

Approvals

The study was approved by the Regional Committee for Medical Research Ethics in Central Norway, the Norwegian Social Science Data Services and the Norwegian Directorate for Health and Social Affairs. The study was conducted according to the Declaration of Helsinki and its later amendments.

Patients and treatment

Patients eligible for the phase II trial were ≥18 years old; had stage I-III disease ineligible for surgery; measurable disease according to RECIST v1.0[11]; no other clinically active cancer; WHO performance status (PS) 0–2; leukocytes $\geq 3.0 \times 10^9$/L; platelets $\geq 100 \times 10^9$/L; bilirubin <1.5× upper limit normal; and creatinine <125 μmol/L. All patients provided written informed consent.

Patients were to receive four courses of cisplatin plus etoposide and were randomly assigned to receive TRT of either 45 Gy in 30 fractions (twice daily—b.i.d.) or 42 Gy in 15 fractions (once daily—o.d.) starting 3–4 weeks after start of the first chemotherapy course. Responders were offered prophylactic cranial irradiation of 30 Gy in 15 fractions. There were no significant differences in overall response rates, progression free survival or overall survival between the treatment arms.[10] Thus, all patients were analysed as one cohort in the present study.

Patients were eligible for the present study if they completed TRT and at least one chemotherapy course and had a CT scan that included the L3 level taken before start of and after chemoradiotherapy.

Assessments

Contrast enhanced computerized tomography (CT) scans were to be taken within 4 weeks before chemotherapy commenced, within 3 weeks after the last course of chemotherapy was administered (response evaluation at Week 12) and during follow-up the first year (20, 28, 36, 44, and 52 weeks after the first course of chemotherapy). A chest X-ray or CT scan was performed on later evaluations. Positron emission tomography CT for staging was not available for LS SCLC patients in Norway when our trial was conducted.

CT scans were analysed using SliceOmatic software, (v.4.3, Tomovision, Montreal, Canada). The total cross-sectional area of skeletal muscle (cm^2) was quantified at the level of the third lumbar vertebra (L3).[12] The first slide from each CT scan at L3 with both vertebral transverse processes clearly visible was used in the analyses. The total cross-sectional skeletal muscle area was identified using well-established thresholds from −29 to +150 Hounsfield units (HU),[6–8] divided by height squared (m^2) and expressed as L3 SMI (cm^2/m^2). SMD was defined as the mean radiodensity measured in HU of the cross-sectional muscle area at the L3 level.

Based on body mass index (BMI) [weight (kg)/height squared (m^2)], patients were categorized as underweight (BMI < 20), normal weight (BMI 20–24.9), overweight (BMI 25–29.9), and obese (BMI ≥ 30).[13] Patient-reported weight loss for the last 3 months prior to diagnosis was categorized as either <5% or ≥5% of the body weight. Stage of disease was assessed according to TNM v7[14] and toxicity according to the Common Terminology Criteria for Adverse Effects v3.0.

Statistical considerations

Survival time was defined as time from inclusion in the study until death of any cause and was estimated using the Kaplan–Meier method and compared using the log-rank test. The *t*-test (SMI and SMD were normally distributed) and Pearson's χ^2 test were used for group comparisons. To investigate whether changes in SMI and SMD were associated with severe treatment toxicity, we used univariable and multivariable logistic regression analyses. Severe treatment toxicity was defined as any Common Terminology Criteria for Adverse Effects Grades 3–4 toxicity. We also performed separate

analyses for the associations with esophagitis, because this is the most frequent toxicity that causes reduced nutritional intake in the present patient population.

To investigate the prognostic impact of SMI and SMD, we used univariable and multivariable Cox regression analyses. In the multivariable analyses, we used separate models for the SMI and SMD analyses. In all models, we adjusted for baseline characteristics (gender, age, PS, stage, BMI, weight loss, and pleural effusion) and TRT schedule. There are no established cut-off values for significant changes in SMI or SMD. Thus, these measures were analysed both as continuous variables and categorized as reduced or stable/increased SMI or SMD. All analyses were two-sided, and the significance level was defined as $P < 0.05$. SPSS v25 or v26 was used for all statistical analyses.

Results

Patients

From May 2005 until January 2011, 157 patients were enrolled in the main trial. Of these, 84 patients were excluded because the CT scans did not include the L3 level (n = 80), due to missing CT scans (n = 3), poor image quality (n = 2), incomplete TRT (n = 3), death during chemoradiotherapy (n = 2), or because the baseline CT scan was performed more than 1 month prior to start of chemotherapy (n = 1). Thus, 68 patients (43.3%) were eligible for the present study (*Figure* 1).

Baseline patient characteristics for all patients are shown in *Table* 1. Median age was 62.9 (range: 43.7–79.5) years, 27 (39.7%) were men, 62 (92.9%) had stage III disease, 11 (16.2%) had PS 2, 3 (4.4%) had loss of appetite, 26 (38.2%) had weight loss ≥5%, 61 (89.7%) completed all four chemotherapy courses, and 39 (57.4%) received TRT of 45 Gy. Median BMI was 24.3 (range: 17–37), 3 (4.4%) were underweight, 37 (54.4%) had normal weight, 19 (27.9%) were overweight, and 9 (13.2%) were obese. There were no significant differences between patients enrolled in the main trial and those analysed in the present study.

Median follow-up was 89.2 months (range: 61–129 months), and 15 patients (22.1%) were alive when the collection of survival data was completed (February 2016).

Changes in skeletal muscle mass and muscle radiodensity

The percentage change in SMI and SMD from baseline until completion of chemoradiotherapy for all patients is shown in *Figure* 2. Median SMI was 44.7 (range: 28.8–72.3) cm^2/m^2 at baseline and 40.6 (range: 28.2–63.0) cm^2/m^2 after treatment. Mean SMI was reduced from 46.25 [95% confidence interval (CI): 44.1–48.4] cm^2/m^2 to 42.13 (95% CI: 40.2–44.1) cm^2/m^2 during the study treatment (mean change: −4.12 cm^2/m^2, 95% CI: 3.06–5.19; $P < 0.001$). Fifty-seven (84%) had a reduction in SMI with a mean reduction of 5.32 (95% CI: 4.3–6.3) cm^2/m^2. Eleven (16%) had a stable or increased SMI with a mean increase of 2.08 (95% CI: 1.0–3.1) cm^2/m^2.

Median SMD was 40.2 (range: 16.3–62.4) HU at baseline and 39.9 (range: 10.0–52.6) HU after treatment. Mean SMD was reduced from 38.40 (95% CI: 36.1–40.7) HU to 37.46 (95% CI: 35.4–39.5) HU during the study treatment (mean change: −0.94 HU, 95% CI: −0.75–2.63; p = 0.272). Thirty-seven patients (54%) had a reduction in SMD with a mean reduction of 5.36 (95% CI: 3.8–6.9) HU. Thirty-one patients (46%) had a stable or increased SMD, with a mean increase of 4.33 (95% CI: 2.4–6.3) HU.

Figure 1 Patient selection. CT, computerized tomography.

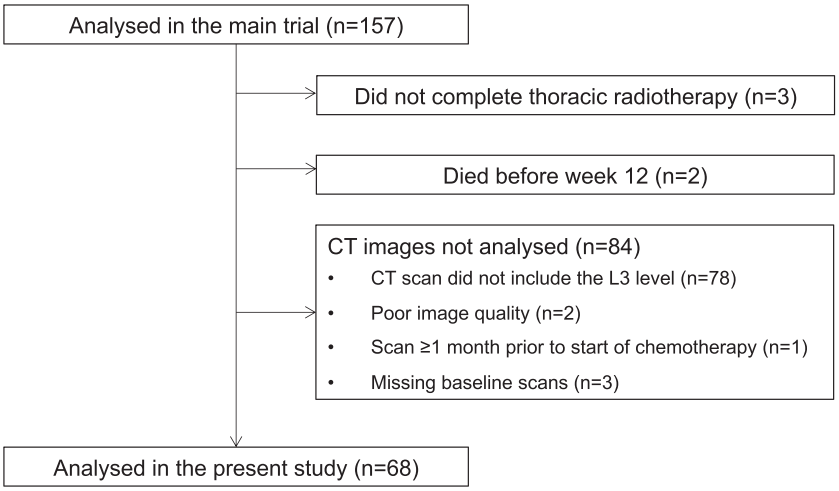
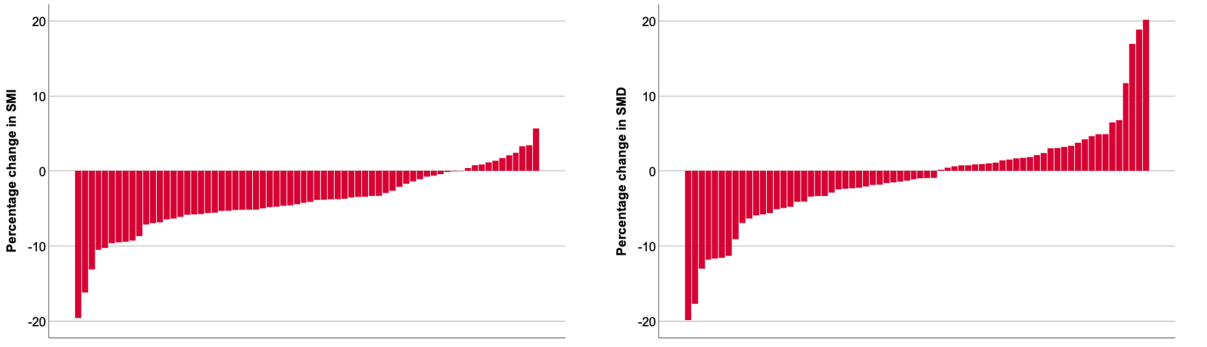


Table 1 Baseline characteristics

Characteristic		Present study (n = 68)		Main trial (n = 157)	
		n	%	n	%
Age, years	Median (range)	62.9 (44–80)		63.3 (40–85)	
Age, ≥75 years		7	10.3	16	10.2
Gender	Male	27	39.7	81	51.6
	Female	41	60.3	76	48.4
Performance status	0	19	27.9	51	32.5
	1	38	55.9	81	51.6
	2	11	16.2	25	15.9
Thoracic radiotherapy	42 Gy/15 fractions	29	42.6	84	53.5
	45 Gy/30 fractions	39	57.4	73	46.5
Completed four courses of chemotherapy	Yes	61	89.7	135	86.0
	No	7	10.3	22	14.0
Prophylactic cranial irradiation	Yes	59	86.8	130	82.8
	No	19	13.2	27	17.2
Stage	I	1	1.5	2	1.2
	II	5	7.4	18	11.5
	III	62	91.2	128	81.5
	Missing	—	—	9	5.7
Pleural effusion	Yes	13	11.0	18	11.5
	No	105	89.0	139	88.5
Body mass index	Underweight (<20.0)	3	4.4	6	3.8
	Normal weight (20 to 24.9)	37	54.4	72	45.9
	Overweight (25.0 to 29.9)	19	27.9	50	31.8
	Obesity (≥30)	9	13.2	29	18.5
Loss of appetite	Yes	3	4.4	7	4.5
	No	63	97.1	144	91.7
	Missing	2	2.9	6	3.8
Weight loss	Yes (≥5%)	26	38.2	42	26.8
	No (<5%)	38	55.4	100	63.7
	Missing	4	5.9	15	9.6
Any Grades 3–4 toxicity	Yes	62	91.2	141	89.8
	No	6	8.8	16	10.2

Figure 2 Percentage changes in SMI (A) and SMD (B) from baseline until completion of chemoradiotherapy. SMD, skeletal muscle radiodensity; SMI, skeletal muscle index.



A) Percent change in skeletal muscle index (SMI)

B) Percent change in skeletal muscle radiodensity (SMD)

Toxicity and changes in muscle measures

Sixty-two patients (91.2%) experienced Grades 3–4 toxicities, including 30 (44.1%) neutropenic infections, 26 (38.2%) radiation esophagitis and 2 (2.9%) radiation pneumonitis. One patient died within 30 days of completion of study treatment from radiation pneumonitis. The proportion with Grades 3–4 toxicity was similar in the overall study population (89.2%).

There were no significant association between Grades 3–4 toxicity and SMI. In the univariable analyses, loss of SMD was

Table 2 Associations between Grades 3–4 toxicity and change in muscle measures

Characteristic	Any Grades 3–4 toxicity						Grades 3–4 esophagitis					
	Univariable		Multivariable (SMI)		Multivariable (SMD)		Univariable		Multivariable (SMI)		Multivariable (SMD)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Loss of SMI[a]	0.93 (0.78–1.11)	0.406	1.07 (0.81–1.41)	0.649	—		1.05 (0.94–1.17)	0.413	1.07 (0.92–1.26)	0.377	—	
Loss of SMD[a]	0.86 (0.75–0.98)	0.027	—		0.87 (0.73–1.03)	0.105	0.91 (0.83–0.99)	0.029	—		0.87 (0.78–0.98)	0.021
Age[a]	0.96 (0.86–1.07)	0.453	0.95 (0.82–1.10)	0.478	0.94 (0.80–1.09)	0.382	0.95 (0.89–1.01)	0.109	0.94 (0.88–1.02)	0.132	0.93 (0.86–1.01)	0.073
Gender												
Female[b]	1		1		1		1		1		1	
Male	0.59 (0.12–3.39)	0.592	1.06 (0.11–10.05)	0.962	0.96 (0.09–10.75)	0.972	0.71 (0.26–1.94)	0.500	0.80 (0.24–2.65)	0.719	0.75 (0.22–2.60)	0.651
PS												
0–1[b]	1		1		1		1		1		1	
2	0.34 (0.05–2.14)	0.250	0.32 (0.03–4.03)	0.381	0.452 (0.04–4.91)	0.514	0.91 (0.24–3.45)	0.889	0.89 (0.18–4.48)	0.883	1.25 (0.23–6.90)	0.795
Disease stage												
I–II[b]	1		1		1		1		1		1	0.143
III	0.00 (0.00- -)	0.999	0.00 (0.00- -)	0.999	0.00 (0.00- -)	0.999	3.38 (0.37–30.68)	0.279	2.70 (0.26–27.57)	0.403	7.30 (0.51–104.19)	
Treatment												
o.d. TRT[b]	1		1		1		1		1		1	
b.i.d. TRT	0.24 (0.03–2.20)	0.208	0.21 (0.02–2.20)	0.191	0.28 (0.03–3.13)	0.300	1.02 (0.38–2.75)	0.964	1.22 (0.38–3.86)	0.740	1.77 (0.50–6.21)	0.376
BMI												
Underweight[b]	1		1		1		1		1		1	
Normal weight	0.00 (0.00- -)		0.00 (0.00- -)		0.00 (0.00- -)		0.96 (0.08–11.66)		0.30 (0.01–6.10)		0.72 (0.04–12.16)	
Overweight	0.00 (0.00- -)		0.00 (0.00- -)		0.00 (0.00- -)		2.22 (0.17–28.86)		0.63 (0.3–15.80)		1.34 (0.7–24.10)	
Obese	0.00 (0.00- -)	0.988	0.00 (0.00- -)	0.940	0.00 (0.00- -)	0.870	1.00 (0.06–15.99)	0.571	0.27 (0.01–9.02)	0.464	0.42 (0.01–12.48)	0.699
Weight loss												
No[b]	1		1		1		1		1		1	
Yes	3.79 (0.42–34.509	0.237	5.90 (0.40–86.80)	0.196	2.39 (0.14–41.93)	0.552	0.73 (0.26–2.05)	0.547	0.68 (0.20–2.32)	0.538	0.44 (0.12–1.57)	0.203
Pleural fluid												
No[b]	1		1		1		1		1		1	0.796
Yes	0.63 80.07–6.269	0.698	0.74 (0.05–11.34)	0.828	0.48 (0.03–7.97)	0.608	1.73 (0.39–7.60)	0.470	1.97 (0.36–10.94)	0.438	1.26 (0.21–7.50)	

BMI, body mass index; CI, confidence interval; OR, odds ratio; PS, performance status; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; TRT, thoracic radiotherapy.
[a]Entered as continuous variables.
[b]Reference categories.

significantly associated with less Grades 3–4 toxicity [odds ratio (OR) 0.86, 95% CI: 0.75–0.98; $P = 0.027$] and less Grades 3–4 radiation esophagitis (OR: 0.91; 95% CI: 0.83–0.99; $P = 0.029$) (*Table* 2). In the multivariable analyses, only the association between less esophagitis and loss of SMD (OR 0.87; 95% CI: 0.78–0.98; $P = 0.021$) remained (*Table* 2). There were no other significant associations between severe toxicity and SMD—or with any of the baseline characteristics.

Survival and changes in skeletal muscle mass and muscle radiodensity

Overall, the median overall survival was 25 months, and the 5 year survival was 27%. Univariable analyses did not show any significant associations between survival and the muscle measures, neither the baseline measures (SMI: $P = 0.321$, SMD: $P = 0.289$) nor the post chemoradiotherapy measures (SMI: $P = 0.087$, SMD: $P = 0.479$). There were also no significant associations in the multivariable analyses (baseline SMI: $P = 0.670$, SMI after chemoradiotherapy: $P = 0.319$; baseline SMD: $P = 0.695$, SMD after chemoradiotherapy: $P = 0.122$).

Univariable and multivariable survival analyses for loss of SMI and SMD are shown in *Table* 3. Loss of SMI was significantly associated with shorter survival in the multivariable analysis [hazard ratio (HR) 1.09; 95% CI: 1.01–1.19; $P = 0.037$], and there was a trend towards an association in the univariable analysis (HR 1.06; 95% CI: 0.99–1.14; $P = 0.094$). Loss of SMD was significantly associated with better survival in both the univariable (HR 0.94; 95% CI 0.90–0.989; $P = 0.006$) and the multivariable analyses (HR 0.94, 95% CI: 0.89–0.99; $P = 0.019$). As an illustration, we have included survival curves for patients with or without a reduction in SMI and SMD in *Figure* 3.

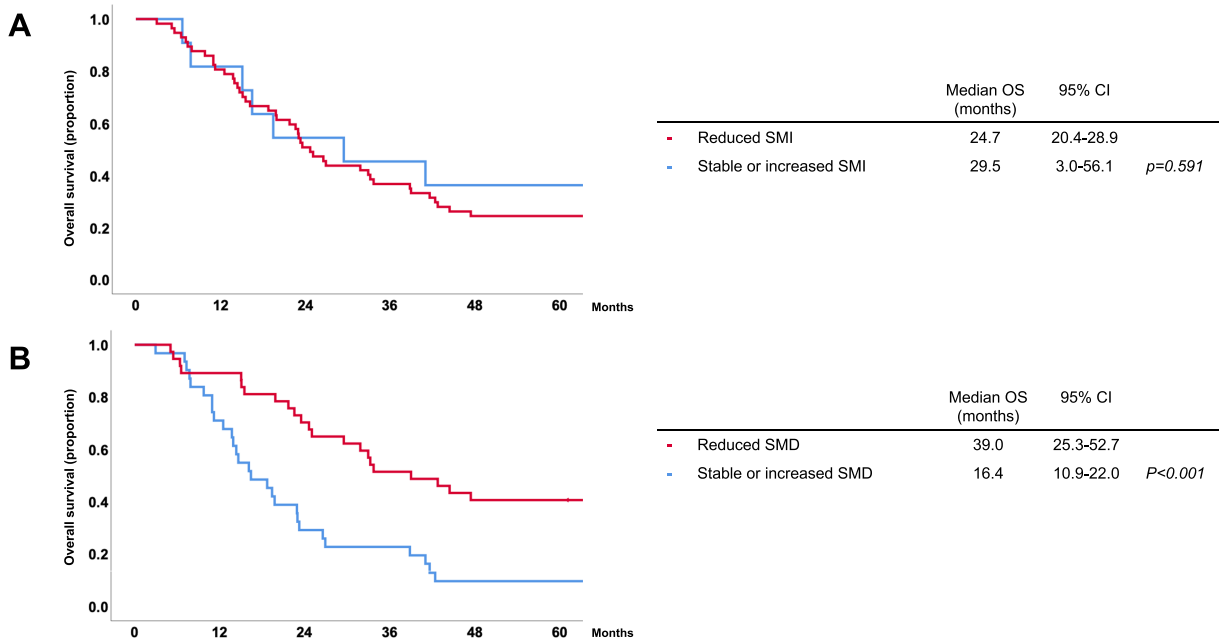
Patients with a normal weight according to BMI had a lower risk of dying compared with underweight patients (HR 0.28, 95% CI: 0.08–0.98; $P = 0.017$) but only in the univariable analysis. None of the other baseline characteristics were significant prognostic factors.

Table 3 Associations between baseline characteristics, muscle measures and survival

Characteristic	Univariable analyses HR (95% CI)	*P*	Multivariable (SMI) HR (95% CI)	*P*	Multivariable (SMD) HR (95% CI)	*P*
Loss of SMI[a]	1.06 (0.99–1.14)	0.094	1.09 (1.01–1.19)	0.037	—	
Loss of SMD[a]	0.94 (0.90–0.98)	0.006	—		0.94 (0.89–0.99)	0.019
Age[a]	1.01 (0.98–1.05)	0.478	1.01 (0.97–1.05)	0.698	1.00 (0.96–1.05)	0.967
Gender						
Female[b]	1		1		1	
Male	0.88 (0.51–1.53)	0.650	0.80 (0.42–1.51)	0.487	0.77 (0.40–1.48)	0.428
PS						
0–1[b]	1		1		1	
2	1.34 (0.65–2.76)	0.423	1.12 (0.49–2.56)	0.789	1.27 (0.52–3.10)	0.605
Disease stage						
I–II[b]	1		1		1	
III	0.96 (0.38–2.42)	0.931	0.85 (0.31–2.32)	0.756	1.81 (0.65–5.10)	0.258
Treatment						
o.d. TRT[b]	1		1		1	
b.i.d. TRT	1.42 (0.81–2.49)	0.217	1.18 (0.65–2.15)	0.591	1.44 (0.76–2.73)	0.269
BMI						
Underweight[b]	1		1		1	
Normal weight	0.16 (0.05–0.57)		0.10 (0.02–0.44)		0.25 (0.06–1.04)	
Overweight	0.28 (0.08–0.98)		0.15 (0.03–0.74)		0.35 (0.08–1.51)	
Obese	0.15 (0.04–0.63)	0.017	0.08 (0.01–0.47)	0.013	0.20 (0.04–1.00)	0.175
Weight loss						
No[b]	1		1		1	
Yes	1.06 (0.61–1.85)	0.845	1.14 (0.59–2.19)	0.698	0.81 (0.42–1.58)	0.535
Pleural fluid						
No[b]	1		1		1	
Yes	0.78 (0.33–1.82)	0.561	1.12 (0.43–2.92)	0.820	0.67 (0.27–1.69)	0.393

BMI, body mass index; CI, confidence interval; OR, odds ratio; PS, performance status; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; TRT, thoracic radiotherapy.
[a]Entered as continuous variables.
[b]Reference categories.

Figure 3 Kaplan–Meier plots for survival split for reduced or stable/increased (A) SMI and (B) SMD. SMD, skeletal muscle radiodensity; SMI, skeletal muscle index.



Discussion

In this study of patients with LS SCLC receiving concurrent chemoradiotherapy, we found a reduction in mean SMI from 46.25 to 42.13 cm^2/m^2 and a reduction in mean SMD from 38.40 to 37.46 HU from baseline until evaluation 2–3 weeks after completion of chemoradiotherapy. Twenty-nine percent had a stable or increased SMI, and 63% had a stable or increased SMD. Loss of SMI during the chemoradiotherapy was significantly associated with shorter survival. Loss of SMD was significantly associated with less Grades 3–4 toxicity, less Grades 3–4 radiation esophagitis and longer survival. There were no other significant associations between the muscle measures and toxicity or survival.

To the best of our knowledge, this is the first study reporting longitudinal muscle measures in a cohort of LS SCLC patients who received standard chemoradiotherapy including an established schedule of TRT, and we are only aware of two other studies investigating the prognostic value of muscle measures in SCLC.[15,16] In the study by Kim *et al.*,[15] only baseline muscle measures were assessed, and contrary to our study, they found that low baseline SMI was an independent prognostic factor for survival. In the study by Nattenmuller *et al.*,[16] 200 patients with all stages of NSCLC and SCLC receiving first line chemotherapy were analysed. The changes in SMI (from 45.7 to 44.3 cm^2/m^2) and SMD (from 38.5 to 36.4 HU) were within the same range as in our study, but they also found that both loss of SMI (HR 1.06; 95% CI: 1.03–1.10; $P < 0.000721$) and SMD (HR 1.02; 95% CI: 1.01–1.03; $P = 0.000884$) were independent negative prognostic factors. The study is, however, not necessarily comparable with ours, because almost all patients (87.5%) had NSCLC and none received chemoradiotherapy.

Our results are supported by studies showing a loss of SMI[9,16–20] and SMD[16–19] during first-line treatment in NSCLC patients. Most studies investigated patients receiving chemotherapy alone but Kiss *et al.*[19] studied stage I-III NSCLC patients receiving chemoradiotherapy. Similar to our study, there were large variations in changes of muscle measures during treatment. Muscle loss was predominant, but Prado *et al.*[20] found that 55.2% of the patients had stable or increased SMI, Stene *et al.*[9] found that 46% of the patients had stable or increased SMI, and in the study by Cortellini *et al.*,[17] 30% of the patients gained muscle mass. None investigated changes in SMD.

A range of studies of several cancer types, including lung cancer, support our findings that loss of SMI[9,16,21–24] is significantly associated with shorter survival. However, contrary to other studies of changes in SMD,[16,23,25–27] patients in our study cohort who had a reduction in SMD had a longer survival than other patients. Although former reports are not consistent, and some reveal no association between change in SMD and survival,[17–19,25,28] this observation contrasts our hypothesis.

Surprisingly, we also found that patients with decreasing SMD experienced less toxicity—including less esophagitis. As this cumbersome side-effect of TRT may lead to decreased nutritional intake, we expected esophagitis to cause a

reduction in both SMD and SMI and potentially have a negative impact on survival. To the best of our knowledge, there are no other studies of associations between changes of SMI or SMD and severe toxicity in cancer patients for comparison, and there are no obvious explanations for our observations. It is, however, possible that symptoms of esophagitis are not always correlated with decreased nutritional intake, and successful nutritional interventions—which we did not collect information about—may have been applied when symptoms of esophagitis occurred.

The majority of LS SCLC patients responds rapidly and well to both chemotherapy and radiotherapy. The response rates are much higher than for most other solid tumours, and we have previously shown that most respond well even to the first chemotherapy course.[29] Thus, it is possible that changes in muscle measures during treatment are less important for the prognosis of LS SCLC than for other malignant diseases. Furthermore, although chemotherapy toxicities such as nausea and anorexia may cause loss of SMI and SMD, severe chemotherapy toxicity has also been shown to be associated with a better prognosis in SCLC.[30,31]

The main limitation of our study is the small sample size. Furthermore, no uniform protocol for the CT scans was applied in this multicentre trial, and different protocols might have influenced the assessment of SMI and SMD.[10] It is, however, the first study to prospectively collect data on muscle measures during treatment and follow-up in patients with LS SCLC receiving standard chemoradiotherapy. Patient characteristics, TNM distribution, overall survival, and 5 year survival are similar to other studies of chemoradiotherapy in LS SCLC,[32–35] we had no restrictions regarding comorbidity or age, and 16.2% had PS 2. The characteristics of the patients included in this subgroup analyses were similar as for the overall cohort in our phase II trial (*Table* 1). Thus, we consider the study population quite representative for LS SCLC patients receiving chemoradiotherapy.

In conclusion, there were large individual variations in changes in muscle measures during chemoradiotherapy, but the majority experienced a loss of both SMI and SMD. Loss of SMI was significantly associated with shorter survival, whereas loss of SMD was significantly associated with less severe toxicity, less esophagitis, and prolonged survival. Thus, the clinical role of assessing changes in SMI and SMD in LS SCLC remains unclear.

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Conflict of interest

C.D.V., T.O.H., M.S., and B.H.G. declare that they have no conflict of interest.

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