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Associations between muscle measures, survival, and toxicity in patients with limited stage small cell lung cancer

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Abstract

Background Standard treatment for patients with limited stage small cell lung cancer (LS SCLC) is concurrent platinum–etoposide chemotherapy and thoracic radiotherapy (TRT). Up to 30% of patients are cured, but severe toxicity is common, and we are not able to identify those who are cured or those who experience severe toxicity before chemoradiotherapy commences. Studies of other cancer patients show that low muscle mass and muscle radiodensity are associated with inferior survival and that a high drug dose per kilogram lean body mass (LBM) is associated with more toxicity, but this has not been investigated in LS SCLC. We analysed patients from a randomized trial comparing two schedules of TRT (n = 157) to investigate the prognostic and predictive role of these muscle measures in LS SCLC.

Methods Patients from a trial comparing once daily hypofractionated with twice daily hyperfractionated TRT were analysed. The skeletal muscle index (SMI), skeletal muscle radiodensity (SMD), and LBM were assessed from baseline computed tomography scans at the L3 level using the SliceOMatic software.

Results Images at the L3 level were available for 122 patients (77.7%). Median age was 64 years, 18% had performance status 2, and 38% had stage III. Grade 3–4 toxicity was observed in 89%, and 5% died from treatment-related side effects. Overall, the median overall survival was 23 months, and the 5 year survival was 25%. Median LBM was 45.2 (range: 16–65) kg, the median SMI 44.8 (range: 29–77) cm^2/m^2, and the median SMD 39.3 (range 16–62) HU. There were no significant associations between survival and any of the muscle measures in the univariable analyses (SMI: P = 0.906, SMD: P = 0.829) or in multivariable analyses adjusting for baseline characteristics (SMI: P = 0.836, SMD: P = 0.260). A higher cisplatin dose per kilogram LBM in the first course significantly increased the risk of grade 3–4 haematological toxicity (P = 0.011) and neutropenic infections (P = 0.012).

Conclusions Patients who received a high dose of cisplatin per kilogram LBM had more haematological toxicity and neutropenic infections than other patients. None of the muscle measures were independent prognostic factors for survival in our cohort of LS SCLC patients who underwent standard chemoradiotherapy.

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

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Introduction

Concurrent cisplatin and etoposide (PE) chemotherapy and thoracic radiotherapy (TRT) is the standard treatment for patients with limited stage small cell lung cancer (LS SCLC). Despite high response rates (80–90%), the 5 year survival is 25–30%.[1,2] Furthermore, the combination of chemotherapy and radiotherapy is associated with severe toxicity,

and treatment-related deaths occur in 2–4%.[1,3] It is a major challenge that we are not able to accurately identify those who are most likely to be cured or those with the highest risk of severe toxicity. Thus, all patients with a good performance status (PS) are offered standard chemoradiotherapy.[1,3–5]

Loss of skeletal muscle mass and loss of muscle quality in terms of fat deposits are common among cancer patients. The whole-body skeletal muscle mass is highly correlated with the skeletal muscle index (SMI) measured at the L3 level, and the skeletal muscle radiodensity (SMD) reflects the degree of fat deposits. Both measures can be assessed from computed tomography (CT) slides using appropriate software (SliceOMatic, Tomovision, Canada).[6–8]

Several studies of cancer patients have shown that both low SMI and SMD are negative prognostic factors[9–12] and that low muscle mass and higher drug doses per kilogram muscle mass (lean body muscle mass, LBM) are associated with severe toxicity from systemic cancer therapy.[13–20] Whether this applies to SCLC patients has scarcely been investigated. One study indicated that low SMI might be a negative prognostic factor also in SCLC patients, but none have reported whether this is the case for SCLC patients with limited stage.[19] Furthermore, the prognostic role of SMD and the impact of higher drug doses per kilogram LBM on toxicity in SCLC patients are not known.

We analysed patients enrolled in a randomized phase II trial comparing two schedules of TRT in LS SCLC.[1] The aims were to investigate whether low SMI and SMD are negative prognostic factors for survival and if high drug doses per kilogram LBM predict severe toxicity in this cohort.

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.

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 1.0[21]; no other clinically active cancer; World Health Organization PS 0–2; leukocytes ≥3.0 × 10^9/L; platelets ≥100 × 10^9/L; bilirubin <1.5 × upper normal limit; and creatinine <125 μmol/L. All patients provided written informed consent.

All patients were to receive four courses of cisplatin [75 mg/m^2 body surface area (BSA) IV day 1] plus etoposide (100 mg/m^2 BSA IV days 1–3), although we recommended not to exceed doses of cisplatin of 165 mg or etoposide of 220 mg corresponding to a BSA of 2.2 m^2. Delays of subsequent courses and dose reductions were recommended if leukocytes were below 2.5 × 10^9/L or platelets were below 75 × 10^9/L on day 22, or if other severe non-haematological toxicity occurred. Patients were randomly assigned to receive TRT of either 45 Gy in 30 fractions [twice daily (BID)] or 42 Gy in 15 fractions [once daily (OD)], starting 3–4 weeks after the start of the first chemotherapy course. Good 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 (OS) between the treatment arms.[1] 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 diagnostic CT scan taken within 4 weeks before the start of treatment that included the L3 level.

Assessments

Computed tomography 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 (L3) vertebra.[22] 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). Radiodensity of the skeletal muscle (SMD) was measured in Hounsfield units (HU). Lean body mass (LBM) was estimated from the equation: Lean tissue (kg) = (0.30 × L3 total cross-sectional area of muscle mass (cm^2)) + 6.06.[7]

The doses of cisplatin and etoposide in milligram per kilogram LBM administered in the first course were calculated. Based on body mass index (BMI) (weight (kg)/height squared (m^2)), patients were categorized as underweight (BMI < 20), normal BMI (20–24.9), overweight BMI (25–29.9), and obese (BMI ≥30).[16]Patient-reported weight loss 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 the TNM v7[23] and toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0. The investigators reported haematological toxicity after each chemotherapy course. The minimum follow-up of blood counts were measurements of haemoglobin, platelets, and leukocytes on days 8, 15, and 22 of each chemotherapy course. Neutropenic infections were defined as any febrile neutropenia or infection while neutropenic during the whole study treatment period.

Statistical considerations

To investigate whether a high drug dose per kilogram LBM was associated with more toxicity, we used univariable and multivariable logistic regression analyses. Four multivariable models were designed. Models 1 and 2 assessed the relationship between grade 3–4 haematological toxicity and milligram per kilogram LBM of cisplatin and etoposide, respectively. Models 3 and 4 assessed the relationship between occurrence of neutropenic infections during the whole study treatment period and milligram per kilogram LBM of cisplatin and etoposide, respectively. All models were adjusted for baseline characteristics (gender, age, PS, stage, BMI, weight loss, and pleural effusion) and TRT schedule. Survival time was defined as time from inclusion until death, was estimated using the Kaplan–Meier method, and compared between groups using log-rank tests.

To investigate the prognostic impact of SMI, SMD, milligram cisplatin per kilogram LBM, and milligram etoposide per kilogram LBM, we used univariable and multivariable Cox regression analyses. In the multivariable analyses, we used separate models for each of these measures and adjusted for baseline characteristics and treatment schedule as described earlier. All analyses were two-sided, and the significance level was defined as $P < 0.05$. SPSS v23 was used for all statistical analyses.

Results

Patients

From May 2005 until January 2011, 157 eligible patients were enrolled in the phase II trial. Thirty-five patients were excluded from the present study due to missing CT scans (n = 3), poor image quality (n = 2), CT scans did not include the L3 level (n = 26), baseline CT scans were obtained more than 1 month prior to the start of chemotherapy (n = 1), or patient did not complete TRT (n = 3). Thus, 122 patients (77.7%) were analysed in the present study (*Figure1*).

Patient characteristics are shown in *Table1*. Median age was 63.7 (range: 40–85) years, 59 (48.4%) were men, 46 (37.7%) had stage III disease, 22 (18.0%) had PS 2, 107 (87.7%) completed all four chemotherapy courses, 59 (48.4%) received TRT of 45 Gy, and 36 (29.5%) had weight loss of ≥5%. Median BMI was 24.6 (range: 15–40); 5 (4.1%) were underweight, 61 (50.0%) had normal weight, 35 (28.7%) were overweight, and 21 (17.2%) were obese.

Median follow-up was 88.2 months (range: 61–129 months), and 26 patients (21%) were alive when collection of survival data was completed (February 2016).

Muscle mass and muscle radiodensity

Body composition data were normally distributed. Median LBM was 45.2 (range: 16–65) kg, the median SMI 44.8 (range: 29–77) cm^2/m^2, and the median SMD 39.3 (range 16–62) HU. Men had a higher SMI than women (median 50.5 vs. 41.8 cm^2/m^2; $P < 0.001$), but there were no significant differences between those ≥75 years of age and those <75 (median 45.0 vs. 44.8 cm^2/m^2; P = 0.689). There was no significant difference in SMD between men and women (median 38.2 vs. 37.3 HU; P = 0.592), but there was a trend towards a difference between patients above 75 years of age and those below (32.4 vs. 39.2; P = 0.073).

Toxicity

One hundred and nine (89.3%) patients experienced grade 3–4 toxicity; 108 (88.5%) developed grade 3–4 haematological toxicity, and 83 (68.0%) grade 3–4non-haematological toxicity. Of these, 54 (44.3%) experienced grade 3–4 neutropenic infections. There were no grade 3–4 thrombocytopenic bleedings.

There were six (4.9%) treatment-related deaths (death within 30 days of completion of study treatment); three (3.5%) died of pneumonitis, one (0.8%) of haemoptysis, one (0.8%) of respiratory failure, and one (0.8%) of acute coronary disease.

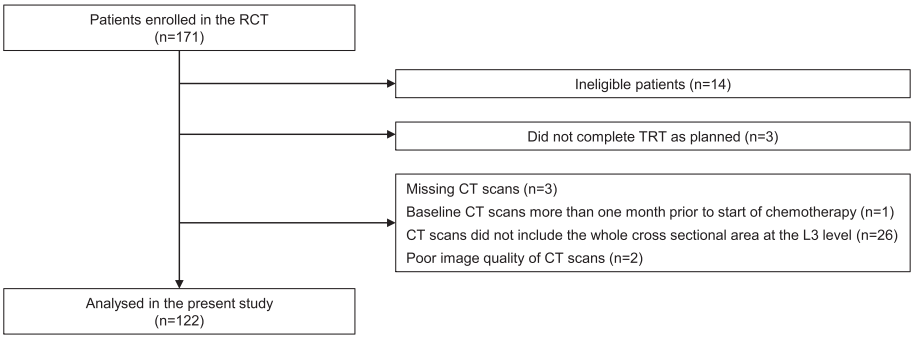

FIGURE 1 Patient selection. CT, computed tomography; RCT, randomized controlled trial; TRT, thoracic radiotherapy.

Table 1 Baseline patient characteristics

		All patients (n = 122)	
		n	%
Age (years)	Median (range)	63.7 (40–85)	
Age (≥75 years)		15	12.3
Gender	Male	59	48.4
	Female	63	51.6
Performance status	0	38	31.1
	1	62	50.8
	2	22	18.0
Thoracic radiotherapy	42 Gy/15 fractions (OD)	63	51.6
	45 Gy/30 fractions (BID)	59	48.4
Completed 4 courses of chemotherapy	Yes	107	87.7
	No	15	12.2
PCI	Yes	102	83.6
	No	20	16.4
Stage	I	15	12.3
	II	57	46.7
	III	46	37.7
	Missing	4	3.3
Pleural fluid	Yes	13	10.7
	No	109	89.3
Body mass index	Underweight (<20.0)	5	4.1
	Normal weight (20 to 24.9)	61	50.0
	Overweight (25.0 to 29.9)	35	28.7
	Obesity (≥30)	21	17.2
Weight loss	Yes (≥5%)	36	29.5
	No (<5%)	75	61.5
	Missing	11	9.0

BID, twice daily; OD, once daily.

Chemotherapy dose per kilogram lean body mass and severe toxicity

The median dose of cisplatin per kilogram LBM in the first chemotherapy course was 3.04 mg (range: 2.00–7.00) mg/kg, while the median dose of etoposide per kilogram LBM was 4.03 mg (range: 2.75–7.67).

According to the univariable analyses, both the cisplatin and etoposide doses per kilogram LBM were significantly associated with grade 3–4 haematological toxicity after the first course of chemotherapy [odds ratio (OR) 2.98, 95% confidence interval (CI) 1.31–6.78; P = 0.009 and OR 1.88, 95% CI 1.06–3.34; P =0 .031, respectively] (*Table2*). The only other factor that significantly predicted toxicity in the univariable analyses was increasing age (OR 1.05, 95% CI 1.01–1.10; P = 0.022) (*Table2*).

In the multivariable models (models 1 and 2, *Table2*), the significant association between grade 3–4 haematological toxicity and milligram cisplatin per kilogram LBM (OR 7.24, 95% CI 1.57–33.39; P = 0.011) remained, and there was a trend towards an association between grade 3–4 haematological toxicity and milligram etoposide per kilogram LBM (OR 2.89, 95% CI 0.99–8.44; P = 0.053). Age was no longer significantly associated with haematological toxicity in any of the models. There was, however, a significant association with male gender according to the model including milligram cisplatin per kilogram LBM (model 1, *Table2*), but not according to the model including milligram etoposide per kilogram LBM. No other significant associations were found.

Univariable analyses also showed a significant association between neutropenic infections and the drug doses per kilogram LBM (cisplatin: OR 2.73, 95% CI 1.25–5.97; P = 0.012, etoposide: OR 1.69, 95% CI 1.00–2.85; P = 0.049) (*Table3*). In the multivariable models, this association remained significant for cisplatin (OR 4.03, 95% CI 1.08–15.10; P = 0.038) (model 3, *Table3*), but not for etoposide (OR 1.62, 95% CI 0.61–4.34; P = 0.335) (model 4, *Table3*). None of the other factors included in the models were significantly associated with neutropenic infections.

Survival

Overall, the median OS was 23 months, and the 5 year survival was 25%. In the univariable analyses, no significant associations between survival and any of the muscle measures (SMI: P = 0.906, SMD: P = 0.829) or the drug doses per kilogram LBM (cisplatin: P = 0.292, etoposide: P = 0.578) were found. Nor were there any significant associations in separate multivariable analyses for each variable (SMI: P = 0.836, SMD: P = 0.260, cisplatin: P = 0.839 and etoposide: 0.198). As an illustration, we have included median OS and survival curves for the quartiles of SMI, SMD, and cisplatin dose per kilogram LBM in *Figure2*.

BMI was the only significant prognostic factor (in the multivariable analysis alone, P = 0.016); patients with a normal weight had a lower risk of dying compared with underweight patients (HR 0.24, 95% CI 0.08–0.72). None of the other baseline characteristics were significant prognostic factors (data not shown).

Discussion

In this study of patients with LS SCLC receiving concurrent chemoradiotherapy, there was a significant association between the chemotherapy dose per kilogram LBM and both haematological toxicity after the first chemotherapy course and neutropenic infections throughout the treatment period. There were no other significant associations between the muscle measures and toxicity or survival.

The observed associations between drug dose per kilogram LBM and severe toxicity correspond well with the results of several other studies showing that a high drug dose per kilogram LBM significantly increases the risk of severe

Table 2 The risk of grade 3–4 haematological toxicity after the first chemotherapy course according to the chemotherapy doses per kilogram lean body mass

			Multivariable analyses			
	Univariable analyses		Model 1		Model 2	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Milligram cisplatin per kilogram LBM[a]	2.98 (1.31–6.78)	0.009	7.24 (1.57–33.39)	0.011	—	—
Milligram etoposide per kilogram LBM[a]	1.88 (1.06–3.34)	0.031	—	—	2.89 (0.99–8.44)	0.053
Age[a]	1.05 (1.01–1.10)	0.022	1.02 (0.96–1.08)	0.557	1.03 (0.97–1.10)	0.324
Gender						
Female[b]	1					
Male	1.38 (0.68–2.82)	0.372	4.05 (1.14–15.75)	0.035	2.87 (0.83–9.90)	0.096
PS						
0–1[b]	1					
2	1.08 (0.43–2.73)	0.865	1.60 (0.50–5.90)	0.458	1.53 (0.46–5.12)	0.494
Disease stage						
I–II[b]	1					
III	1.42 (0.47–4.26)	0.537	2.01 (0.38–2.41)	0.309	2.19 (0.59–8.20)	0.244
Treatment						
OD TRT[b]	1					
BID TRT	1.06 (0.52–2.16)	0.866	1.43 (0.52–3.30)	0.462	1.10 (0.45–2.70)	0.838
BMI						
Underweight[b]	1					
Normal weight	1.89 (0.29–12.12)	0.335	2.68 (0.12–59.31)	0.150	3.45 (0.18–65.16)	0.097
Overweight	1.26 (0.19–8.50)		1.81 (0.77–42.70)		2.30 (0.11–46.03)	
Obese	0.75 (0.10–5.58)		0.58(0.02–15.14)		0.68 (0.03–15.23)	
Weight loss						
No[b]	1					
Yes	0.59 (0.27–1.32)	0.201	0.41 (0.15–1.16)	0.093	0.45 (0.17–1.23)	0.118
Pleural fluid						
No[b]	1					
Yes	1.28 (0.40–4.05)	0.676	1.15 (0.27–4.99)	0.845	1.32 (0.33–5.34)	0.698

BID TRT, twice daily thoracic radiotherapy; BMI, body mass index; CI, confidence interval; LBM, lean body mass; OD TRT, once daily thoracic radiotherapy; OR, odds ratio; PS, performance status.
[a]Entered as continuous variables.
[b]Reference categories.

haematological toxicity in cancer patients.[18,20,24,25] None of these studies investigated whether there was an association with neutropenic infections, but it seems reasonable that a higher frequency of haematological toxicity increases the risk of neutropenic infections.

We are aware of only one other study investigating the prognostic value of muscle measures in SCLC.[19] In this Korean study of 149 patients with all stages of SCLC, they defined low SMI using established cut-off values from the definition of sarcopenia (SMI of <55 cm^2/m^2 for men and <39 cm^2/m^2 for women),[26] and contrary to our study, they found that low SMI was an independent prognostic factor for survival (HR 1.68, 95% CI 1.04–2.72; $P = 0.034$). When applying Korean cut-off values (49 cm^2/m^2 for men and 31 cm^2/m^2 for women) in the same cohort, there was still a numerical difference in OS, but the difference was not statistically significant (8.4 vs. 12.7 months; $P = 0.144$). This study is, however, not necessarily comparable with our study. In the Korean study, 67.8% of the patients had extensive disease, there were more men (85.2% vs. 48.4% in our study), more elderly (67.1% vs. 40.2% above 65 years of age), fewer (29.5% vs. 100%) received chemoradiotherapy, and 20.8% received supportive care only. The median follow-up time was shorter than in our study (29.0 vs. 88.2 months). Furthermore, they did not measure SMD. Several studies indicate that SMD is a more important prognostic and predictive muscle measure than SMI.[12,16] Finally, we analysed SMI and SMD as continuous variables, which is recommended for studies on prognostic factors[27] and due to the lack of well-established global cut-off values for abnormally low SMI and SMD.[6,15]

Our results contrast a number of studies showing that low SMI and low SMD are significantly negative prognostic factors in patients with a wide range of types of cancer.[9–11,13–16,19,20,28–31] However, most previous studies have investigated advanced cancer patients receiving palliative treatment. Both the response rate to standard treatment (80–90%) and the 25–30% 5 year survival are much higher for LS SCLC than for most other solid tumours. Thus, the potentially negative impact of low muscle mass or poor muscle quality from cancer might be overcome by the better response to treatment.

Another possible explanation may be that LS SCLC patients have less cancer-induced muscle depletion, but when comparing with results of one of our previous studies of Norwegian advanced NSCLC patients[12] with the present data, there were no large differences in SMI (median 43.3 vs.

Table 3 The risk of neutropenic infection during the study treatment according to the chemotherapy doses per kilogram lean body mass

			Multivariable analyses			
	Univariable analyses		Model 3		Model 4	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Milligram cisplatin per kilogram LBM[a]	2.73 (1.25–5.97)	0.012	4.03 (1.08–15.10)	0.038	—	—
Milligram etoposide per kilogram LBM[a]	1.69 (1.00–2.85)	0.049	—	—	1.62 (0.61–4.34)	0.335
Age[a]	1.01 (0.97–1.06)	0.510	1.03 (0.97–1.10)	0.309	1.04 (0.98–1.11)	0.200
Gender						
Female[b]	1					
Male	0.38 (0.18–0.80)	0.010	0.67 (0.21–2.11)	0.488	0.45 (0.14–1.41)	0.171
PS						
0–1[b]	1					
2	0.53 (0.20–1.40)	0.199	0.41 (0.12–1.42)	0.159	0.40 (0.12–1.33)	0.135
Disease stage						
I–II[b]	1					
III	1.21 (0.40–3.65)	0.734	1.50 (0.36–6.34	0.581	1.52(0.38–5.41)	0.559
Treatment						
OD TRT[b]	1					
BID TRT	0.66 (0.32–1.35)	0.257	0.82 (0.32–2.11	0.684	0.63 (0.26–1.57)	0.325
BMI						
Underweight[b]	1					
Normal weight	3.18 (0.34–30.10)	0.718	—[c]	0.760	—[c]	0.747
Overweight	3.78 (0.38–37.28)		—[c]		—[c]	
Obese	3.00 (0.29–31.63)		—[c]		—[c]	
Weight loss						
No[b]	1					
Yes	0.69 (0.31–1.55)	0.367	1.01 (0.36–2.87)	0.983	1.10 (0.40–3.01)	0.849
Pleural fluid						
No[b]	1					
Yes	1.09 (0.34–3.45)	0.885	0.44 (0.10–2.97)	0.280	0.52 (0.13–2.11)	0.360

BID TRT, twice daily thoracic radiotherapy; BMI, body mass index; CI, confidence interval; LBM, lean body mass; OD TRT, once daily thoracic radiotherapy; OR, odds ratio; PS, performance status.
[a]Entered as continuous variables.
[b]Reference categories.
[c]Not evaluable due to small number of cases.

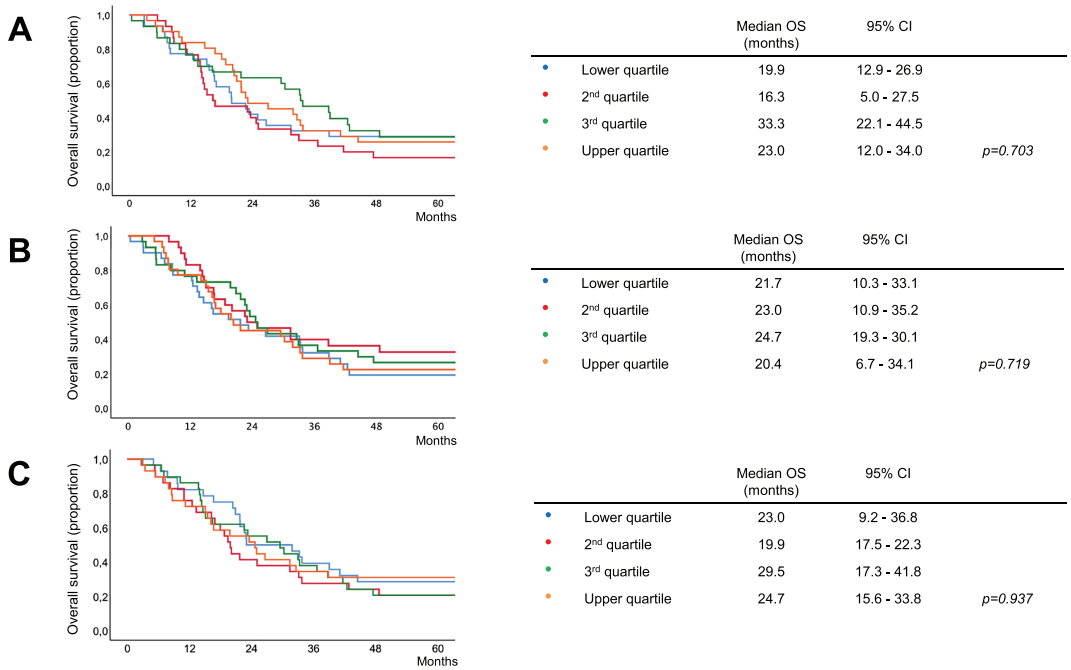

FIGURE 2 Kaplan–Meier survival plots according to (*A*) quartiles of skeletal muscle index, (*B*) quartiles of skeletal muscle radiodensity, and (*C*) quartiles of milligram cisplatin per kilogram lean body mass. *P*-values were calculated using the log-rank test. CI, confidence interval; OS, overall survival.

44.8) or SMD (37.3 vs. 39.3 HU), although NSCLC and LS SCLC patients are not necessarily comparable. SCLC is considered a more rapidly progressing disease, and the proportion of smokers is higher in SCLC.[32,33]

The relatively small sample size is the main limitation of our study. It is, however, the first study to prospectively collect data on muscle measures and weight loss in patients with LS SCLC receiving standard chemoradiotherapy. Patient characteristics, TNM distribution, OS, and 5 year survival are similar to other studies of chemoradiotherapy in LS SCLC,[3,4,34,35] we had no restrictions regarding comorbidity or age, and 18.0% had PS 2. Thus, we consider the study population representative for LS SCLC patients receiving chemoradiotherapy.

Our findings support the evidence that a high drug dose per kilogram LBM increases the risk of haematological toxicity and neutropenic infections. It has been suggested that the dose of cytotoxic chemotherapy should be adjusted according to LBM.[25] However, this may not be appropriate for LS SCLC patients. There were no deaths clearly related to the chemotherapy or shorter survival among the patients with the highest drug dose per kilogram LBM, suggesting that the increased toxicity had no impact on survival. Furthermore, there are indications that patients who are given a high standard dose of chemotherapy when treatment commences have a longer survival than those who are offered lower doses,[36] and other studies have shown that lung cancer patients who experience chemotherapy-induced haematological toxicity live longer than those who do not.[37,38] Considering that at least 25% of patients are cured, LS SCLC patients may accept more toxicity than those who receive palliative systemic therapy. An alternative to lowering the chemotherapy doses would be to administer G-CSF, which reduces the risk of neutropenic infections. The role of G-CSF is, however, not established in LS SCLC, because a randomized trial showed that G-CSF increases toxicity from TRT,[39] although this was not found in a recent subgroup analysis of a large randomized trial comparing TRT of 45 Gy in 30 fractions and 66 Gy in 33 fractions in LS SCLC.[40]

There are no obvious explanations for the weaker association between dose per kilogram LBM and neutropenic infections for etoposide than cisplatin. However, etoposide more frequently causes neutropenia/neutropenic infection and may cause neutropenic infection also when the dose per kilogram LBM is low, possibly weakening the association with neutropenic infections. Another explanation may be differences in pharmacokinetics, but our study was not designed to assess such differences.

In conclusion, patients who received a high chemotherapy dose per kilogram LBM had more haematological toxicity and neutropenic infection. However, they did not have a shorter OS, suggesting that all patients with LS SCLC should receive standard concurrent chemoradiotherapy regardless of their baseline SMI and SMD.

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Conflict of interest

None declared.

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