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Original article

Peripheral but not axial muscle mass is associated with early mortality in bone metastatic lung cancer patients at diagnosis

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Objectives. – Identification of sarcopenia is a key issue in oncology. Several methods may be used to evaluate muscle mass in patients. Routine cancer follow-up computed tomography (CT) provides axial muscle mass whereas whole-body densitometry (DEXA) measures appendicular lean mass (ALM). Up to now, no studies have assessed, in cancer patients, the correlation between CT and DEXA muscle mass indicators and compared their prognostic value.

Methods. – We included patients with synchronous bone metastases from lung adenocarcinoma at diagnosis. Diagnosis was confirmed by bone biopsy. Skeletal muscle area was determined semi-automatically on initial CT scan at the T7, T12, and L3 vertebral level using Osirix® software. The skeletal muscle index (SMI) was calculated as the ratio of muscle area to height squared. Standardised ALM/height squared data were obtained by DEXA assessment within a 30-day window of CT.

Results. – A total of 65 patients were included; 47 (72%) were male. Mean \pm SD age was 65 ± 11.4 years. DEXA was available for 46 patients. The performance status was good (< 1) for 39 patients. SMI indicators were significantly correlated with each other (ρ from 0.3 to 0.7) but moderately correlated with ALM (ρ from 0.1 to 0.7). ALM had a good discriminatory ability on 6-month survival (AUC 0.87 [0.76; 0.97]). ALM was associated with early mortality (< 6 months) (HR = 0.29, 95% CI [0.15; 0.57]; $P < 0.001$) but not with later mortality (> 6 months). In contrast, no significant effect was found for SMI.

Conclusions. – Peripheral muscle mass (standardized ALM by DEXA) but not axial muscle mass (SMI assessed by CT) was associated with early mortality (< 6 months) suggesting that cancer-induced muscle loss would affect differently appendicular muscles and axial muscles.

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1. Introduction

According to the 2019 consensus of the European Working Group on Sarcopenia in Older People (EWGSOP2), sarcopenia is a muscle disease defined by a low muscle strength resulting from low muscle quantity and altered muscle quality leading to impaired

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physical performance which is an indicator of severity. Sarcopenia can be caused by age, inflammatory or malignant diseases, low level of physical activity, and reduced food intake [1]. In cancer patients, sarcopenia is associated with cachexia [2,3], worse survival [4], increased risk of toxicity from systemic cancer therapy [5], and postoperative morbidity in surgical oncology [6]. The prevalence of sarcopenia is higher among lung cancer compared to other types of cancer patients [7], and muscle mass loss has been reported as a prognostic factor in lung cancer, independently of the tumor stage in two recent meta-analysis [4,8].

There are several imaging options available for body composition assessment including magnetic resonance imaging, ultrasonography, dual-energy X-ray absorptiometry (DEXA), and computed tomography (CT) [9]. CT and DEXA are both internationally recommended in oncology [3]. CT is routinely used for investigations and follow-up in lung cancer patients and thus offers an easy opportunity to simultaneously assess muscle mass loss by calculating the skeletal muscle mass index (SMI) [10]. Skeletal muscle area assessed from a single central body CT slice located at the third lumbar level (L3), is closely correlated with the estimated total lean body skeletal muscle mass [11]. It has become the most commonly used method in studies including cancer patients according to the international working group on sarcopenia [12]. Other vertebral levels have also been used to quantify sarcopenia, notably thoracic CT scans. A good correlation of SMI measurements between the thoracic and L3 levels has been found [13]. Alternatively, DEXA is the most commonly used method to assess muscle mass and detect sarcopenia in aging patients with 44% of the sarcopenia studies as reported in a recent literature review [14]. Initially, the ROSETTA study, including a population of elderly people and conducted by Baumgartner et al., has defined sarcopenia using only Appendicular Lean Mass divided by size square (ALM), a quantitative standardized index obtained by whole-body DEXA scan. Thus, sarcopenia was defined as an ALM lower than sex-specific cut-off values: 7.26 kg/m² for men and 5.45 kg/m² for women [15].

Only a few previous studies have assessed the correlation between the trunk muscle mass (SMI evaluated using CT) and the limb muscle mass (ALM evaluated using DEXA). The results of these studies are discordant [16,17]. Moreover, no study has compared the prognostic value of ALM and SMI among an oncological population of bone metastatic patients. From a clinical point of view, that is a relevant question because:

- all lung cancer patients undergo CT and if the CT is efficient, it would avoid adding additional examination – DEXA remains the gold standard – to assess sarcopenia;
- because the two technics do not assess the same muscle groups: axial muscle for CT and appendicular muscle for DEXA.

Interestingly, we gathered, some years ago, a prospective cohort (POUMOS) of synchronous bone metastatic lung adenocarcinoma patients in which a large number of patients underwent whole-body DEXA in addition to the CT assessment [18]. Regarding the oncological prognostic, it is a homogeneous group of patients with synchronous bone metastases who did not receive any systemic bone or cancer therapy at the time of evaluation and who did not receive immune checkpoint inhibitors. Thus, we built an ancillary study of POUMOS aiming to describe muscle indicators in these patients. The main aim of the study was to assess the independent prognostic value of ALM by DEXA vs. SMI-L3 measured by CT on the 6-month and 12-month survival of patients with synchronous bone metastases from lung adenocarcinoma. Second aims were the correlations between the SMI (T7, T12 and L3) and the ALM, and the prognostic value of SMIT7 and SMIT12 in these patients.

2. Methods

2.1. Study design

The POUMOS study (“*cancer du POUmon et Métastases OSseuses*”) is a non-interventional, single center, prospective study including a cohort of patients with synchronous bone metastases from lung adenocarcinoma (ClinicalTrials.gov ID: NCT02810262). The cohort was handled through collaboration between rheumatologists (CC), thoracic oncologists (NG), radiologists (JBP, JR, CD), and pathologists (MB, ED) from the University Hospital of the Hospices Civils de Lyon, France. The study was approved by the local ethics committee (Institutional Review Board No. 11263 – CPP Sud-Est II). All included patients received clear information and signed a written consent.

The inclusion and exclusion criteria in the POUMOS prospective cohort, and the clinical, laboratory, and radiological data, as well as histological analysis after percutaneous or surgical biopsy have been previously reported [18,19]. Briefly, patients with a suspected first bone metastasis from lung cancer underwent a complete clinical, biological, DEXA and radiological evaluation. All patients had a percutaneous biopsy of one bone metastasis under computed tomography (CT) scan guidance or surgical procedure. Patients with confirmed diagnosis of bone metastasis from lung adenocarcinoma were included. Patients who had previously received systemic oncological treatment with chemotherapy or tyrosine kinase inhibitors were excluded. The current study is a secondary analysis of our cohort. For this study, we included the patients from the POUMOS cohort who underwent a CT scan or a PET scan for the diagnostic of the inaugural bone metastasis, allowing the exploration of the L3 level.

2.2. Data collection

2.2.1. Clinical data

A questionnaire was used to prospectively collect clinical data in a secured database [18]. It included questions regarding demographic data (sex, age) and general parameters (performance status (PS), activity level, body mass index (BMI), recent body weight loss, smoking history). The PS was evaluated using the Eastern Cooperative Oncology Group score (ECOG) [20]. The activity level was categorized into three groups: restricted physical activity (group 1), regular walk (group 2), and sporting activity (group 3). Recent weight loss was defined as a loss of at least 2 kg within the last 6 months.

Data regarding lung cancer and bone metastasis related variables were collected. They consisted in the histological parameters, the molecular genotyping of activating alterations in oncogenic drivers including epidermal growth factor receptor (EGFR) and Kirsten-RAS (KRAS), the number of bone metastases, and the localization of bone metastases on weight bearing bone.

Data regarding systemic treatments and anti-osteoporotic treatment history (bisphosphonate or denosumab) were collected. The therapeutic strategy including the use of an antiresorptive treatment (bisphosphonate or denosumab) was collected during follow-up.

2.2.2. Serum measurements

Patients underwent fasting blood withdrawal at 8:00 am. Immediate standard biological serum measurements were centralized in our institution laboratory. Cell count (lymphocyte and neutrophil count, in G/L), creatinine (in $\mu\text{mol/L}$), calcium (Ca, in mmol/L), albumin (Alb, in g/L), C-reactive protein (CRP, in mg/L) levels, and glycated hemoglobin (HbA1c, in %) were assessed following routine procedure. The corrected calcemia (cCa) was computed according to the formula $cCa = Ca + (40 - Alb)/40$ in mmol/L. Hereafter, calcemia

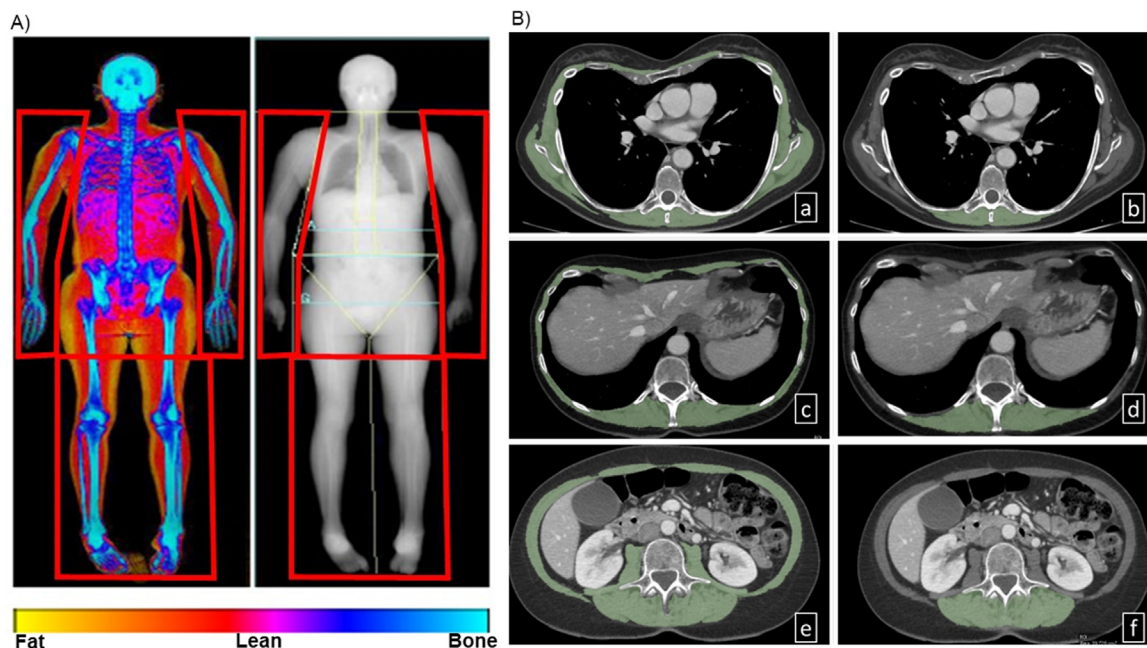


Fig. 1. A. Whole-body densitometry (DEXA) image. Framed in red is the appendicular lean mass used for calculation of appendicular lean mass (ALM). B. Measurement of the skeletal muscle area using an axial CT slice. Segmentation (green) at T7, T12, and L3 level of total skeletal muscle surface [(a), (c), and (e), respectively], and paravertebral muscle surface [(b), (d), and (f), respectively].

will refer to corrected calcaemia. Emerging combined inflammation scores to predict survival in advanced lung cancer were calculated as the neutrophil/lymphocyte ratio (NLR) [21], and the advanced lung cancer inflammation index ($ALI = BMI \times Alb/NLR$) [22].

2.2.3. Muscle mass assessment using DEXA

Whole-body DEXA scan (Discovery[®], Hologic, Bedford, MA USA) was performed for all the patients able to sustain – ability to lay down on the table with acceptable pain – the DEXA scan in order to determine the standardized ALM as the sum of the lean mass of the four limbs divided by the height squared (kg/m^2) (Fig. 1A).

Patients who did not undergo whole-body DEXA scan examination with the determination of ALM within 30 days from the CT were not included in the DEXA-related analysis.

2.2.4. Muscle mass assessment using CT

2.2.4.1. CT image acquisition. CT examinations of thoracic and abdominal cavities were performed using one of the following scanners: GEMINI TF TOF16[®] (Philips Healthcare, Netherlands), Brilliance 64[®] (Philips Healthcare, Netherlands), BrightSpeed (GE Healthcare, United States), or Revolution GSiV (GE Healthcare, United States). Unenhanced series were used for the study. The acquisition parameters were standardized as follow: 120 kV, adaptive mAs, pitch of 0.75 with 3 mm slice thickness reconstructed every 2 mm.

2.2.4.2. Post-processing. Image data from CT scan were fully anonymized and axial slices were exported from the picture archiving and communication system (PACS system, Centricity, GE Healthcare, United States) to a MacOS X[®] (version 10.5.8) station for analysis. Segmentation of the muscles was performed by a trained junior radiologist with 4 years of experience blinded to patient data (CD) using Osirix[®] version 5.0 software (Pixmeo SARL, Switzerland) [23] (Fig. 1B). Muscular segmentation was performed according to the standard process as previously reported [16,24]. This technic uses a threshold applied on unenhanced images. Once the segmentation has been done by the machine, sections are visually checked for

quality control and eventually corrected by the radiologist investigator.

Since it was an exploratory study, we wanted to rule out the hypothesis that muscle mass index may vary because of spine location. Thus, we decided to select an axial oblique image at the 7th thoracic (T7) – semi-rigid segment-, the 12th thoracic (T12) – junctional segment-, and the 3rd lumbar (L3) vertebra showing the entire transverse processes (mobile segment). At the T7 level, the segmented total skeletal muscle surface comprised the erector spinae, latissimus dorsi, external and internal inter-costal, pectoralis major, serratus anterior muscles and teres major, subscapularis, infraspinatus muscles, and the deltoid muscle at variable degree. At the T12 level, the segmented total skeletal muscle surface comprised the erector spinae, latissimus dorsi, external and internal oblique, rectus abdominis, external and internal inter-costal muscles [25]. At the L3 level, the segmented total skeletal muscle surface comprised the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal oblique, and rectus abdominis muscles. Similarly, at each level we also segmented the paravertebral muscle group surface comprising the erector spinae and transversospinales muscles, plus the trapezius muscle at the T7 level.

The SMI at the level T7 (SMI T7), T12 (SMI T12), and L3 (SMI L3) were calculated by dividing the segmented total skeletal muscle surface of each level by the height squared [1]. Similarly, the paravertebral SMI (SMIp) at each level (SMIp T7, SMIp T12, and SMIp L3) were calculated by dividing the paravertebral muscle group surface by the height squared.

Interobserver reproducibility has been assessed on 28 consecutive patients and shows an intraclass correlation coefficient (ICC) of 0.971. This excellent correlation was consistent with previously reported studies [26].

2.3. Statistical analyses

Continuous variables were expressed as mean \pm standard deviation (SD), and categorical variables as count (percentage). In order to take into account the difference related to sex, muscular mass

biomarkers were standardized by reducing and centering using each sex mean and standard deviation. Variables denoted “.sd” were standardized according to sex. Correlations between muscular mass biomarkers were analyzed using a non-parametric Spearman coefficient and its 95% confidence interval (95% CI), and represented using a correlation plot. Correlation was categorized as high positive (0.7 to 0.9), moderate positive (0.5 to 0.7), low positive (0.3 to 0.5), or negligible (0 to 0.3).

The parameters reported as independent prognostic factors for metastatic lung cancer in previous studies were assessed: PS, age at diagnosis, sex, smoking status, and cachexia diagnosis [27,28]. The oncological factors cited were the mutation status [29], the use of systemic chemotherapy, or the prescription of an anti EGFR therapy [30]. The bone parameters were calcemia, the number of metastases or bone metastases of the limbs, complications of fractures, and treatment with Denosumab [30–32]. The inflammatory parameters were hyperneutrophilia and CRP value [33], NLR [34] and ALI [22].

The analysis of prognostic factors was performed using multivariate Cox models; the effect of each factor on the hazard of death was quantified using the hazard ratio (HR) and the associated 95% CI. The proportional hazard (PH) assumption was assessed visually using Schoenfeld residuals. Only ALM broke the PH assumption, and was therefore studied using a time-split Cox model with two hazard ratios for ALM, one for the effect before 6 months and the other one for the effect after 6 months (univariate and multivariate analysis) [35]. The CT mass biomarker with the HR the farthest from 1 in univariate analysis was retained for the multivariate analysis. A separate multivariate model was built for ALM in patients with an available DEXA scan. Adjustments were performed on age, PS and variables with the highest *P*-value in univariate analysis, with a limitation to 6 variables considering the need for 5 to 10 events per variable. In addition, for reasons of collinearity, NLR was chosen over hyperneutrophilia and ALI in the multivariate analysis. A sensitivity analysis was performed by studying SMIT7 and SMIT12 in multivariate analysis for all the patients using the same method, and by studying CT biomarkers for the patients who underwent DEXA scan. A *P*-value strictly inferior to 0.05 was considered as significant. Analyses were performed using R software, version 3.6.1 (R Core Team, <https://www.r-project.org/>).

The ability of each of muscular mass biomarker to predict the 6- and 12-month survival (as a binary variable) was analyzed quantitatively, without threshold, using receiver operating characteristic (ROC) curves to determine the area under curve.

3. Results

3.1. Population characteristics

From the POU MOS cohort, 65 patients had a CT scan at baseline. Among them, 62 (95%) had an exploitable CT for the present analysis and 46 (71%) underwent whole-body DEXA scan examination within 30 days from CT exploration.

There were 47 (72%) male patients. The mean \pm SD (range) age of the included patients was 64.9 ± 11.4 (36–90) years. PS was good (i.e. 0 or 1) for nearly two-third of the patients (64%) (Table 1). The median [IQR] follow-up duration was 7.5 [2.2–14.8] months. The overall median [95% CI] survival was 7.9 [5.7–10.1] months.

The average BMI was 24.0 ± 4.3 . A total of 30 (47%) patients experienced a recent loss of weight. Only 2 (3%) patients had mixed lesions and also 2 (3%) sclerotic lesions. All other patients had osteolytic bone metastases. No patient had previously received any oncological or antiresorptive treatments (including zoledronic acid and denosumab) in the last 10 years. After diagnosis, 86% patients

were prescribed a systemic antiresorptive treatment: 49% received zoledronic acid, and 37% received denosumab (Table 1).

3.2. Characteristics of CT and DEXA muscle mass index

The mean \pm SD ALM was 7.5 ± 1.0 kg/m² among male patients and 5.7 ± 1.2 kg/m² among female patients. The mean \pm SD SMIL3 was 49.7 ± 6.8 cm²/m² among male patients and 40.6 ± 8.7 cm²/m² among female patients (Table S1).

ALM was moderately correlated with SMI (Spearman coefficient, ρ): ALM with SMI L3, $\rho=0.6$; ALM with SMIT12, $\rho=0.7$; and ALM with SMIT7, $\rho=0.5$ (Fig. 2).

BMI was highly correlated with ALM ($\rho=0.8$), but poorly with SMI (mean $\rho=0.3$), and with SMIP (mean $\rho=0.15$, Fig. 2).

SMI L3 was moderately correlated with SMIT7 ($\rho=0.6$) as well as with SMI T12 ($\rho=0.6$).

Regarding the paravertebral index, SMIP7, SMIP12, and SMIP13 were moderately correlated with each other (mean $\rho=0.5$), and poorly correlated with ALM ($\rho=0.3$) and SMIs ($\rho=0.4$; Fig. 2).

3.3. Survival analysis

3.3.1. Univariate and multivariate analysis of muscle mass parameters associated with increased risk of mortality

In univariate analysis, among the 46 patients for whom whole-body DEXA scan was available, the ALM predictive performance of mortality rate was different over time. ALM was strongly associated with early mortality (<6 months) (HR = 0.34, 95% CI [0.20; 0.56]; $P < 0.01$), but not with long-term mortality (>6 months) (HR = 0.86 95% CI [0.50; 1.50]; $P = 0.60$; Table 2).

This association remained highly significant in multivariate analysis after adjustment for age, PS, NLR, active smoking state, and hypercalcemia, which are independent prognostic factors of metastatic lung cancer and associated with survival in our univariate analysis (Table 3). ALM was strongly associated with early mortality -before 6-month- (ALM multivariate before 6-month, HR = 0.29, 95% CI [0.15; 0.57]; $P < 0.05$), but not with long-term mortality -after 6-month- (ALM multivariate after 6-month, HR = 0.74, 95% CI [0.40; 1.37]; non-significant). The difference in the prediction effect of ALM before and after 6-month was significant ($P < 0.05$).

Considering the specific ALM cut-off values reported by Baumgartner et al. [15], sarcopenic patients had a hazard of death 2.7-fold higher (HR = 2.7, 95% CI [1.38; 5.31]; $P < 0.01$) than non-sarcopenic patients.

Considering the univariate analysis, SMI indicators were not significantly associated with survival (SMIT7: HR = 0.78, 95% CI [0.57; 1.05]; non-significant; SMIT12: HR = 0.85, 95% CI [0.64; 1.12]; non-significant; SMIL3: HR = 0.78, 95% CI [0.58; 1.05]; non-significant; Table 2). SMI L3, which is the most recognized indicator, was not associated with survival in multivariate analysis (HR = 0.79, 95% CI [0.56; 1.10]; non-significant; Table 3).

A complementary sensitivity analysis showed that SMIL3 was not associated with survival in the population of patients who underwent a DEXA scan. SMIT7 and SMIT12 were not associated with survival in multivariate analysis, in the whole population.

3.3.2. Survival curves and ROC analysis: prognostic performance in 6- and 12-month survival prediction

ALM had a high ability for 6-month survival prediction (AUC 6-month = 0.87 [0.76; 0.97]). This ability was much smaller for 12-month survival (AUC 12-month = 0.68 [0.51; 0.85]).

SMIT7, SMIT12, and SMIL3 had a lower discriminatory power at 6-month (AUC range from 0.60 to 0.67) and similar range at 12-month (AUC range from 0.57 to 0.68), within the same range as BMI (AUC 6-month = 0.67 [0.53; 0.81], AUC 12-month = 0.63 [0.48; 0.78]; Fig. 3A and B). Survival curves in the population split into 2

Table 1

Baseline characteristics of the 65 (unless otherwise stated) included patients with a CT scan at baseline and according to sarcopenic whole-body densitometry (DEXA) status when available.

Population characteristics	n = 65	Sarcopenic n = 20	Non-sarcopenic n = 26	No DEXA n = 19
Clinical				
Sex (male)	47 (72%)	15 (75%)	21 (81%)	11 (58%)
Age (years)	64.9 ± 11.5	63.10 ± 14.21	64.77 ± 9.76	67.11 ± 10.67
PS (n = 61)				
0	11 (18%)	5 (25%)	3 (13%)	3 (17%)
1	28 (46%)	8 (40%)	14 (61%)	6 (33%)
2	15 (25%)	6 (30%)	5 (22%)	4 (22%)
3	5 (8%)	1 (5%)	1 (4%)	3 (17%)
4	2 (3%)	0 (0%)	0 (0%)	2 (11%)
Physical activity (n = 59)				
Group 1	26 (44%)	10 (53%)	9 (39%)	7 (41%)
Group 2–3	33 (56%)	9 (47%)	14 (61%)	10 (59%)
BMI (kg/m ²)	24.1 ± 4.2	21.0 ± 3.7	26.07 ± 3.1	24.5 ± 4.5
Recent loss of weight (> 2 kg in 6 months)	30 (47%)	11 (55%)	11 (44%)	8 (42%)
Active smoking				
Never	12 (18%)	5 (25%)	3 (11%)	4 (21%)
Former	33 (51%)	9 (45%)	15 (58%)	9 (47%)
Active	20 (31%)	6 (30%)	8 (31%)	6 (32%)
Oncological				
Adenocarcinoma	65 (100%)			
Molecular status				
Other	32 (49%)	11 (55%)	11 (55%)	10 (53%)
EGFR mutant	13 (20%)	6 (30%)	4 (20%)	3 (15%)
KRAS mutant	11 (17%)	2 (10%)	5 (25%)	4 (21%)
N/A	9 (14%)	1 (5%)	0 (0%)	2 (11%)
Bone-related				
Bone metastasis number by bone scan (n = 62)				
1	5 (8%)	0 (0%)	3 (12%)	2 (11%)
2 to 5	17 (27%)	7 (39%)	5 (20%)	5 (26%)
> 5	40 (65%)	11 (61%)	17 (68%)	12 (63%)
Weight bearing bone metastasis (n = 59)	26 (44%)	10 (56%)	9 (36%)	7 (44%)
Initiation of antiresorptive treatment after inclusion (n = 51)	44 (86%)	13 (68%)	20 (80%)	2 (33%)
Zoledronic acid	25 (49%)	10 (67%)	8 (35%)	7 (54%)
Denosumab	19 (37%)	4 (25%)	13 (57%)	2 (17%)
Laboratory				
Lymphocytes (G/L)	1.9 ± 2.2	2.7 ± 3.9	1.6 ± 0.6	1.6 ± 0.4
Neutrophils (G/L)	7.4 ± 3.9	9.1 ± 4.9	6.4 ± 2.7	6.8 ± 3.5
NLR	5.0 ± 4.8	6.2 ± 7.6	4.3 ± 1.8	4.8 ± 3.3
CRP (mg/L)	60.3 ± 67.1	71.4 ± 79.9	55.5 ± 66.2	55.0 ± 54.5
Alb (g/L)	34.0 ± 5.7	33.1 ± 6.9	35.8 ± 5.3	32.7 ± 4.2
HbA1c (%)	5.8 ± 0.6	5.4 ± 0.4	6.0 ± 0.7	5.8 ± 0.7
cCa (mmol/L)	2.3 ± 0.2	2.3 ± 0.2	2.3 ± 0.1	2.3 ± 0.2
Creatinine (μmol/L)	71.7 ± 25.8	68.6 ± 16.0	79.8 ± 33.1	64.2 ± 20.8

Data are expressed as mean ± standard deviation (SD) or count (percentage).

Alb: albuminemia; BMI: body mass index; cCa: corrected calcemia; CRP: C-reactive protein; CT: computed tomography; EGFR: epidermal growth factor receptor; HbA1c: glycated hemoglobin; KRAS: Kirsten-RAS; NLR: neutrophil/lymphocyte ratio; PS: performance status.

groups according to the median in each gender for BMI, SMIL3 by CT and ALM by DEXA are presented in Fig. 3C, D and E.

4. Discussion

Our study highlighted that ALM assessed using DEXA at diagnosis was a major independent short-term (<6-month) overall survival predictor in bone metastatic lung adenocarcinoma patients who had a still good preserved general condition. On the contrary, no prognostic value of CT biomarkers was found in these patients. CT enables the analysis of central muscle mass and DEXA the analysis of peripheral muscle mass. Moreover, the study included a homogeneous cohort of patients in terms of oncological prognosis, and was thus suited for the investigation of the performances of the different muscle mass index obtained using CT and DEXA.

In the present study, SMIL3 was not an independent prognostic factor. This is in line with results from other cohorts of patients with advanced non-small-cell lung carcinoma (NSCLC) who had still good preserved general condition [36], but contradictory to other studies showing a significant negative impact of low muscle mass determined by similar assessments [4,8]. The correlation

between SMIL3 and ALM was moderate, whereas SMIL3, SMIT12, and SMIT7 had stronger correlation with each other. By contrast, the more restrictive SMIp were weakly correlated with the other indicators representative of overall muscle mass. In fact, CT and DEXA assess different groups of muscles: axial musculature for CT and peripheral lean mass for DEXA. This suggests that sarcopenia could affect heterogeneously different groups of muscles at the inaugural stage of cancer diagnosis.

From a physiopathological perspective, systemic causes would theoretically lead to “homogeneous” muscle mass loss. Some of the systemic causes are cancer-related inflammation, insufficient protein ratio secondary to anorexia, or in this specific bone metastasis setting, high circulating TGFβ. Indeed, TGFβ can be released from osteolytic bone metastasis during osteoclast-mediated bone destruction. TGFβ induces oxidative stress and leads to skeletal muscle weakness [37]. The systemic causes of muscle loss have to be balanced by physical activity stimulating some specific muscle groups. It is therefore reasonable to hypothesize that patients who are diminished but not bedridden could continue to use their postural-tone-muscles, such as the erector muscles of the spine, the shoulder girdle, or the abdominal strap (all taken into account by SMIs on

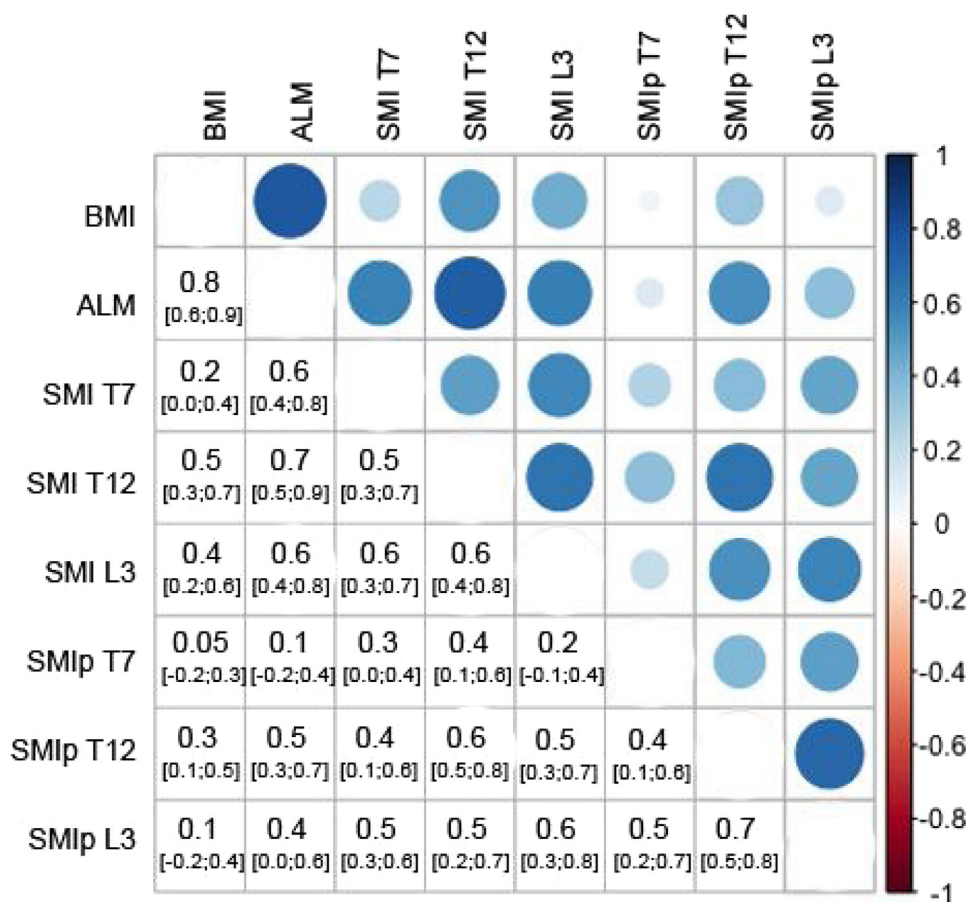


Fig. 2. Spearman correlation graphic. The bigger and darker the circle, the stronger the correlation. ALM: standardized appendicular lean mass by whole-body densitometry (DEXA) in kg/m²; SMI: skeletal mass index by computed tomography in cm²/m²; SMlp: paravertebral muscles.

the scanner) but exert a minimal solicitation of the active motor muscles, especially the legs. According to our hypothesis, the least solicited muscle groups would first suffer the consequences of inflammation and undernutrition. These considerations will have to be assessed in future studies.

In other conditions than cancer, studies comparing CT and DEXA biomarkers are scarce and equivocal. When dealing with the same muscle territory, studies have showed a high correlation between biomarkers considering appendicular muscle in a geriatric cohort [38], or the whole-body fat and fat-free mass [16]. On the contrary, when central and peripheric muscle territories have been explored, the correlation was moderate. This result gives weight to the physiopathological hypothesis outlined above. SMI and ALM comparison has also been reported in a study including 59 non-bedridden adults eligible for liver transplantation, showing that SMIL3 was only weakly correlated with ALM, but none of the technics was discriminant for overall survival [17].

Overall, survival results at 6 and 12 months are interesting. Even if the number of alive patients at 12 months was limited, results highlighted the difficulty to predict long-term survival at care initiation in such synchronous bone metastatic lung cancer patients. Indeed, many aspects of these patients should be simultaneously evaluated such as the molecular profile of the tumor, bone metastasis fracture risk, musculoskeletal condition, and cachexia, in order to provide personalized medicine program [39]. Our study supports that muscle mass and sarcopenia are important survival parameters and that they should be considered at diagnosis. Only a holistic approach of such patients can potentiate tumor treatment and improve their survival. Following this general approach,

we are fully aware that we did not appraise sarcopenia *stricto sensu*: indeed, its definition includes a decrease in muscle function as well as in muscle mass. At the time of the study, such a functional approach was not common, and we were not able to test the muscle function nor assess physical activity through questionnaires. But following the updated EWGSOP2 definition of sarcopenia [1], performing functional tests (grip strength or chair stand measure) in future studies would be relevant. Indeed, muscle function has been consistently shown to be a more powerful predictor of clinically relevant outcomes than muscle mass alone [40,41]. This will certainly strengthen again the holistic approach.

In this study, we choose to evaluate muscle mass through two different imaging modalities. The gold standard to assess sarcopenia (muscle mass) is the DEXA that provides the index ALM/size² [15]. As named, it assesses appendicular muscle mass. Advantage: it is an automatic, reproducible and reliable evaluation performed during whole-body DEXA. The clinical issue is that it is not performed in daily practice by oncologists and that it adds an X-ray examination to frail patients with already a complicated schedule. By contrast, all these cancer patients undergo a regular chest-abdomen-pelvis CT scan for cancer staging and follow-up. Thus, the idea was to evaluate whether we could take advantage of the available chest-abdomen-pelvis CT scan to assess muscle mass. Currently this technic was not well documented in this indication and remained time consuming for radiologists. Moreover, the muscles available on this CT are paravertebral muscles and not appendicular. We aimed to be pragmatic and there was a high relevance for patients to compare this CT-technic to the gold standard

Table 2
Univariate analyses for parameters associated with death.

Parameters	HR	[95%CI]
Clinical		
Age (per year increase)	1.01	[0.98; 1.04]
Sex (female)	0.92	[0.51; 1.69]
Active smokers	2.19**	[1.22; 3.94]
Restricted physical activity (group 1 vs. 2–3)	2.00*	[1.13; 3.53]
Poor PS (≥ 2)	1.27	[0.71; 2.25]
EGFR mutation	0.75	[0.38; 1.47]
Oncological		
Visceral metastasis	2.11	[0.64; 6.94]
> 5 scintigraphic bone metastases	1.32	[0.73; 2.38]
Hypercalcaemia (> 2.55 mmol/L)	2.03*	[1.09; 3.79]
Bone-related		
Biphosphonate	1.50	[0.86; 2.62]
Denosumab	0.66	[0.37; 1.19]
Hyperneutrophilia (per 1 G/L increase)	1.14***	[1.07; 1.23]
NLR (per 1 SD increase)	1.11***	[1.05; 1.17]
Inflammatory		
ALI (> 23.2)	0.44**	[0.25; 0.78]
CRP (per 1 mg/L increase)	1.00	[1.00; 1.01]
Overweighted BMI > 25 kg/m ²	0.54*	[0.3; 0.97]
Body weight loss (per 1 kg increase)	1.17	[0.68; 2.03]
Nutritional		
Hypoalbuminemia (< 35 g/L)	0.97	[0.93; 1.02]
HbA1c (per 1% increase)	0.61*	[0.38; 0.98]
SMIT7 (per 1 SD increase)	0.78	[0.57; 1.05]
SMIT12 (per 1 SD increase)	0.85	[0.64; 1.12]
SMIL3 (per 1 SD increase)	0.78	[0.58; 1.05]
SMIP7 (per 1 SD increase)	1.01	[0.48; 2.11]
Muscular mass biomarkers		
SMIP12 (per 1 SD increase)	0.58	[0.24; 1.41]
SMIP L3 (per 1 SD increase)	0.50	[0.19; 1.32]
ALM ^a (per 1 SD increase) with early mortality (< 6 months)	0.35***	[0.21; 0.58]
ALM ^a (per 1 SD increase) with long-term mortality (> 6 months)	0.86	[0.50; 1.50]
Sarcopenia ALM ^a (< 7.26 kg/m ² for male, < 5.45 kg/mv for female)	2.71**	[1.38; 5.31]

PS: performance status; EGFR: epidermal growth factor receptor; NLR: neutrophil lymphocyte ratio; ALI: advance lung cancer inflammation index; CRP: C-reactive protein; HbA1c: glycated hemoglobin A1c; ALM: standardized appendicular lean mass by DEXA in kg/m²; SMI: skeletal mass index by computed tomography in cm²/m²; SMIP: paravertebral muscles; HR: hazard ratio; SD: standard deviation; 95% CI: 95% confidence interval. Significant results appear in bold.

^a Available for 46 patients.

* $P < 0.05$.

** $P < 0.01$.

*** $P \leq 0.001$.

DEXA one. To compare appendicular muscle mass index obtained by DEXA and CT scan is a different research question that deserve to be tackle in further protocols.

Our study has several limitations. First, the limited size of the cohort may reduce statistical power to demonstrate that SMIL3 can predict survival. Second, to date, there is no validated CT muscle mass reference value. Indeed, muscle loss is not a uniform condition, and also depends on race, age, sex, muscle use, and physical activity. The reported thresholds are thus variable [42]. Nevertheless, the cohort of patients studied herein was quite homogenous in terms of physical characteristics and cancer conditions. Future studies with longitudinal follow-up should overcome sarcopenia biomorphometric issue. A third limit is that DEXA could not be performed in all patients because of patient limitations such as pathologic fracture or severe pain preventing them from being positioned in the DEXA machine. Because of the rapid muscle mass variation during patient care, we privileged a strict compliance to assess ALM at diagnosis within the 30 days of the CT. This allowed to maintain a certain homogeneity in the cohort. Since the reasons for not performing the DEXA were acute skeletal related events and not chronic illness, we believe that the study bias is therefore limited. Our results underline that comprehensive approach including tumor molecular profile, general patient condition, bone fracture

Table 3

Multivariate model for parameters associated with death with SMI L3 (A) and (B). Parameters are expressed per 1 SD increase.

Parameters	HR	[95% CI]
With death with SMI L3		
Age	1.73*	[1.09; 2.74]
Poor PS (≥ 2)	1.83	[0.94; 3.56]
NLR	2.00***	[1.47; 2.72]
Active smokers	3.34***	[1.61; 6.96]
Hypercalcaemia	2.14	[0.96; 4.76]
SMI L3	0.79	[0.56; 1.10]
With ALM		
Age	1.47	[0.94; 2.29]
Poor PS (≥ 2)	1.38	[0.53; 3.59]
NLR	2.00***	[1.47; 2.85]
Active smokers	4.04**	[1.58; 10.3]
Hypercalcaemia	2.15	[0.77; 5.97]
ALM with early mortality (< 6 months)	0.29***	[0.15; 0.57]
ALM with late mortality (> 6 months)	0.74	[0.40; 1.37]

PS: performance status; NLR: neutrophil lymphocyte ratio; ALM: standardized appendicular lean mass by DEXA in kg/m²; SMI: skeletal mass index by computed tomography in cm²/m²; HR: hazard ratio; SD: standard deviation; 95% CI: 95% confidence interval. Significant results appear in bold.

* $P < 0.05$.

** $P < 0.01$.

*** $P \leq 0.001$.

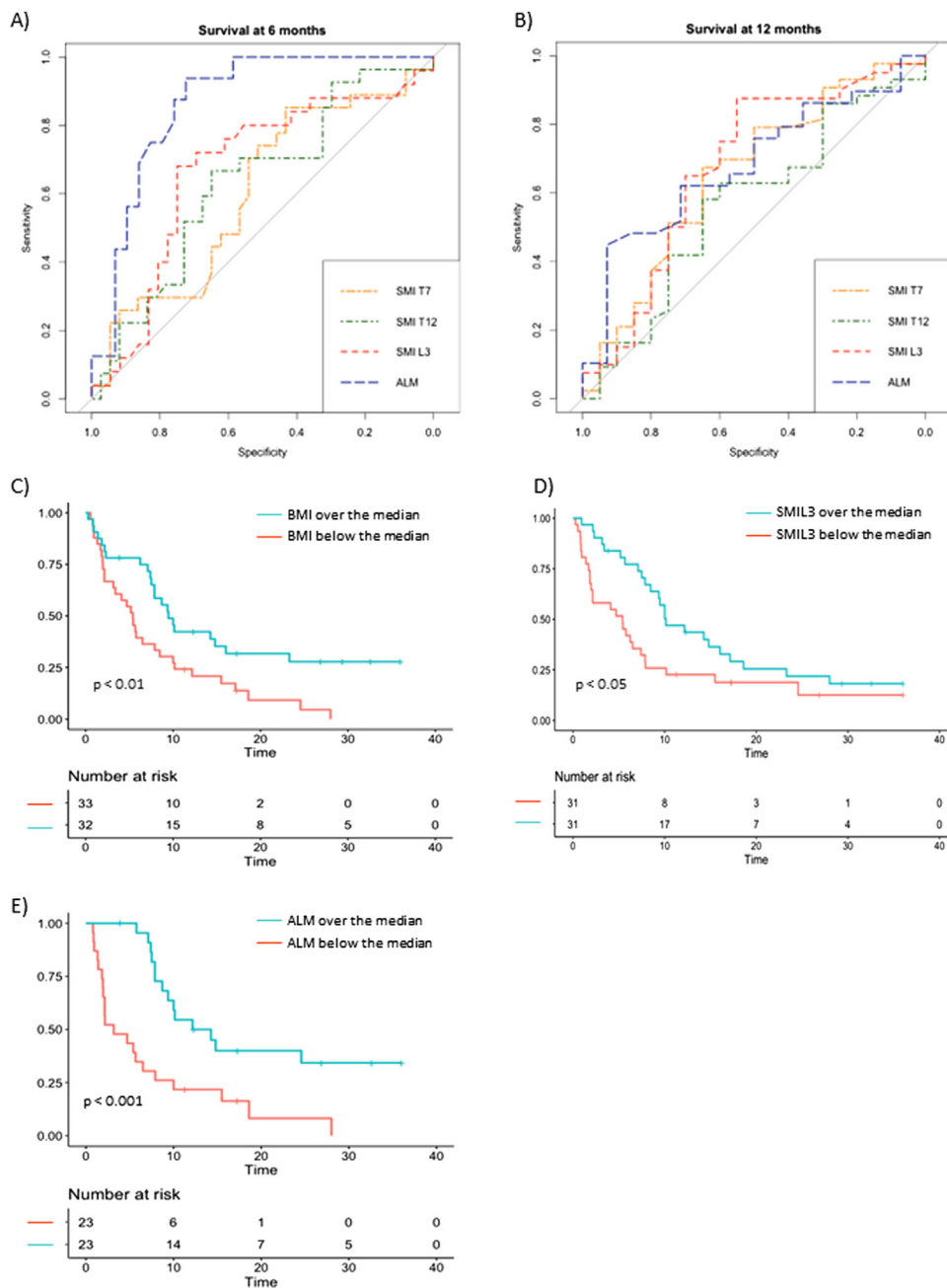


Fig. 3. Receiver operating characteristic analysis for ALM. (A) Area under curve graphic for 6-month overall survival prediction and for 12-month overall survival prediction (B). Survival curves (Log Rank test) in the population split into 2 groups according to the median in each gender for BMI (C), SMIL3 (D) and ALM (E). ALM standardized appendicular lean mass by whole-body densitometry in kg/m²; BMI body mass index; SMIL3 skeletal muscle mass index by computed tomography in cm²/m² at the level of L3 vertebra.

risk, and muscle status is crucial to provide personalized medicine and improve patient survival.

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Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data (Table S1) associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.jbspin.2023.105613>.

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