ORIGINAL RESEARCH LETTER

A practical measurement of thoracic sarcopenia: correlation with clinical parameters and outcomes in advanced lung cancer

To the Editor:

Sarcopenia, the loss of skeletal muscle mass, is common in chronic disease, and has been hypothesised to contribute to fatigue and breathlessness [1, 2]. The research gold standard for assessing sarcopenia relies on whole-body, cross-sectional imaging, an impractical approach in routine care [3]. A more practical alternative measures lumbar skeletal muscle density at L3 using computed tomography (CT) normalised for height, termed the skeletal muscle index (SMI) [4]. While evidence suggests that reduced lumbar SMI correlates with adverse clinical outcomes, such as mortality in lung or colorectal cancers [5], little research has explored how this measure of sarcopenia relates to breathlessness or exercise tolerance.

Although patients with lung cancer and respiratory disease often receive thoracic CT scans as part of their care, fewer patients receive abdominal CT scans. This limits the ability to assess sarcopenia using lumbar SMI and thus there is a need to explore the utility of thoracic SMI as a measure of sarcopenia. In addition, a measure of the skeletal muscle of the chest, being involved in the work of breathing, may correlate better with breathlessness and functional capacity. Therefore, we sought to determine the feasibility of measuring sarcopenia using thoracic SMI, measured at T4 (tSMI). We also aimed to explore the relationship between tSMI and L3 SMI (lSMI), breathlessness and 6-min walk test (6MWT) distance in a cohort of patients with advanced nonsmall cell lung cancer (NSCLC).

We conducted a secondary analysis of data from a prospective, observational cohort study involving 97 patients with stage 4 NSCLC, which contained measures of cachexia, physical performance and patient-reported outcomes, the details of which are reported elsewhere [6–9]. Longitudinal assessments included a comprehensive symptom inventory containing a 0–10 numerical rating scale (NRS) for breathlessness severity over the past 7 days [10], a standard 6MWT measuring distance and exertional breathlessness on a Borg scale, and hand-grip strength using a Jamar dynamometer (Patterson Medical, Warrenville, IL, USA). We included handgrip strength in our models according to consensus definitions of sarcopenia [3]. We obtained three handgrip measurements in each hand, using the highest value for our analysis. We analysed CT scans that the treating oncologists obtained as part of their routine care and utilised the first visit for each patient in which there was a corresponding CT scan within 30 days.

Calculation of the tSMI was adapted from the lSMI described by Prado *et al.* [11]. We measured the cross-sectional area of skeletal muscle (cm^2) at the T4 level, as suggested in the software manual, using Slice-O-Matic software V4.3 (Tomovision, Magog, QC, Canada), dividing by height squared (m^2) to yield the tSMI ($cm^2 \cdot m^{-2}$). We defined handgrip weakness according to validated cut-offs: <20 kg for women and <30 kg for men [3].

To explore for associations between tSMI ($cm^2 \cdot m^{-2}$), breathlessness severity (NRS and post-6MWT Borg scale) and 6MWT distance, we used a generalised linear model adjusting for age, sex, smoking status in pack-years, diagnosis of chronic obstructive pulmonary disease (COPD) and handgrip weakness. We analysed survival using Cox proportional hazards models. In a secondary analysis, we explored the correlation between tSMI and lSMI, and explored the association between lSMI and the outcomes of interest using the same statistical procedures in the subset of patients with corresponding lumbar scans available. Missing data were not imputed and only complete records were used in regression models. The original study and this analysis were approved by the Duke Institutional Review Board (Duke University, Durham, NC, USA).

86 patients met the inclusion criteria; 11 were excluded because of missing data or not having a thoracic CT scan within 30 days of a corresponding study visit. Mean±SD age was 62.8±9.6 years; 36 (42%) were female; and 68 (79%) were Caucasian, and 14 (16%) were African American. Mean±SD tSMI was 60.9±3.7 $cm^2 \cdot m^{-2}$. tSMI was significantly higher in men (65.4±13.4 $cm^2 \cdot m^{-2}$) than in women (54.5±11.5 $cm^2 \cdot m^{-2}$; $p<0.001$). The average Karnofsky performance score was 73±11.9. 12 (14%)

participants were current smokers, 61 (71%) were former smokers, and mean±SD smoking history was 52.5±38.5 pack-years. 16 (19%) people had COPD, and 3 (3%) had congestive heart failure. The mean±SD 6MWT distance for participants was 373±114 m. Median (95% CI) survival was 11.5 (7.0–13.1) months.

After adjusting for age, sex, pack-years of smoking, presence of COPD and handgrip weakness, we found no significant association between tSMI and breathlessness severity in the past 7 days (table 1). The associations between tSMI, exertional breathlessness and 6MWT distance were also not significant. We found no statistically significant difference in unadjusted survival between those with normal and reduced handgrip strength (p=0.48). Similarly, a Cox proportional hazards model with the same adjustments as above did not demonstrate a significant relationship between survival and tSMI or handgrip weakness (p=0.66 and 0.36, respectively). A sensitivity analysis excluding handgrip weakness (using tSMI alone) demonstrated similar results for all end-points. The addition of race and current chemotherapy also produced similar nonstatistically significant results with poorer precision due to missing data.

Finally, using the same procedures, we identified 50 patients with eligible lumbar scans and found similar results. lSMI decreased in a nonstatistically significant manner over time (p=0.06). In those patients with corresponding lumbar and thoracic scans (n=26), there was a moderate relationship between tSMI and lSMI (Pearson correlation coefficient=0.60). Similar to tSMI, we found no significant relationships between lSMI and hazard for death, breathlessness, exertional breathlessness and 6MWT distance.

Our findings suggest that a definition of sarcopenia based on tSMI does not correlate with breathlessness, exercise capacity or survival in a small sample of patients with advanced NSCLC. This is despite a dramatic survival difference in a prior analysis when stratified by presence of cancer anorexia–cachexia syndrome [7]. The strengths of the current study include a well-characterised population with complementary measures of sarcopenia, breathlessness and exercise tolerance, and a robust exploratory analysis. Despite negative results, we demonstrated the feasibility of measuring sarcopenia using tSMI.

We were limited by a small sample size and missing data; while a larger sample would provide more power to detect significant associations, our findings suggest a small magnitude of effect. We used CT scans obtained in the routine processes of care, which may not meet the rigorous standards of prospective research. Variation in CT scan quality may bias our results towards the null. Furthermore, we could not account for the severity of COPD and other comorbidities in our models to potentially improve the precision of our models.

Perhaps T4 is not the optimal level at which to measure the tSMI. Although measurement at T4 provides information about accessory muscles of respiration, including the pectoralis, intercostals and scalenes, it does not capture the diaphragm. Perhaps diaphragmatic function is preserved despite loss of other skeletal muscles. Alternatively, the chest wall muscles may actually hypertrophy to attempt to compensate for the increased work of breathing, such that patients' increasing tSMI may correlate with the severity of their breathlessness [12]. Future studies should explore whether such practical measures of sarcopenia correlate with outcomes in non-malignant respiratory diseases, which may have different mechanisms of breathlessness than NSCLC [13].

In conclusion, the proposed measure of thoracic sarcopenia (tSMI) did not correlate with breathlessness, exercise tolerance or survival in our sample of patients with advanced NSCLC. Nonetheless, we demonstrated that sarcopenia assessment using routine CT scans is feasible. The importance of identifying a pragmatic way to measure sarcopenia and how this relates to breathlessness cannot be overstated. Such a measure would help elucidate the complex interplay between skeletal muscle, airway dynamics, neurophysiology and other important contributing mechanisms to progressive breathlessness in advanced respiratory disease [14].

TABLE 1 Associations between each 10 $cm^2 \cdot m^{-2}$ increase in tSMI or lSMI and death, NRS breathlessness, post-6MWT breathlessness (Borg) and 6MWT distance[#]

	tSMI	lSMI
Subjects n	86	50
Death hazard ratio (95% CI)	0.94 (0.70–1.26)	0.97 (0.57–1.64)
Breathlessness (0–10, NRS)	0.08 (p=0.80)	0.82 (p=0.18)
Exertional breathlessness (Borg)	0.02 (p=0.96)	0.56 (p=0.42)
6MWT distance m	−0.57 (p=0.96)	−18.1 (p=0.54)

Data are presented as β-coefficients, unless otherwise stated. tSMI: thorax skeletal muscle index; lSMI: lumber skeletal muscle index; NRS: numerical rating scale; 6MWT: 6-min walk test. [#]: adjusted for age, sex, pack-years of smoking, presence of chronic obstructive pulmonary disease and handgrip weakness.

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