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Enhancing Evaluation of Sarcopenia in Patients with Non-Small Cell Lung Cancer (NSCLC) by Assessing Skeletal Muscle Index (SMI) at the First Lumbar (L1) Level on Routine Chest Computed Tomography (CT)

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Abstract

Purpose—Ongoing cancer cachexia trials evaluate sarcopenia by skeletal muscle index (SMI) at the L3 vertebrae level, commonly used as a standard. Routine chest CT institutional protocols widely differ in including L3. We investigated whether SMI at L1 assessment, rather than L3, would be reliable and more practicable for NSCLC.

Methods—NSCLC patients with routine CT chest had SMI measurements performed at L1 using Slice-O-Matic software. Accuracy of including L1 level, imaging quality and ability to detect sarcopenia was collected and correlation of L1 SMI with BMI was performed.

Results—37 patients with NSCLC (73 CT assessments) were enlisted at three institutions. Characteristics: 47% female; medians: age 59, KPS 80%; BMI 25.49, weight 72.97 kg, SMI 59.24. Sarcopenia was detected in 14.7% of patients; 20% had sarcopenic obesity. Of the 73 CTs, 94.5% included L1 (95% CI 86.6%–98.5%). Three images (4%) were difficult to evaluate. Inclusion of L1 was similar among the three participating institutions (90.4% to 96.7% inclusion). BMI correlation with SMI was weak (r = 0.329).

Conclusions—SMI assessment at L1 is achievable in patients with NSCLC receiving routine chest CT, with 96% having acceptable quality evaluations. Similar to results previously reported at L3, BMI showed poor correlation and low sensitivity to detect muscle mass loss. The use of CT at

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Conflict of interest
Authors indicated no potential conflict of interest.

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L1 is reliable and presents the opportunity for easier patient evaluation of sarcopenia in patients with lung cancer without the need for additional testing or radiation exposure.

Keywords

Lung cancer; sarcopenia; cachexia; skeletal muscle mass; chest CT; L1

Introduction

Cancer anorexia-cachexia syndrome, including skeletal muscle wasting, is a key aspect affecting survival and quality of life of cancer patients [1]. Definitions for these terms vary and at times can be controversial [2]. Nonetheless, it has been widely accepted that *sarcopenia*, defined as loss of skeletal muscle mass, is a major component of cancer cachexia [3]. Sarcopenia is an independent predictor of poor quality of life, increased chemotherapy toxicity, lower response to treatment, shorter time to tumor progression, prolonged length of stay and post-operative complications and decreased quality of life and survival in numerous different malignancies with ample supportive evidence [4–8]. As is the case with other cancers, sarcopenia in lung cancer has been shown to be associated with similarly poor outcomes [9–13]. This study was initiated to document a practical approach to assess early sarcopenia in non-small cell lung cancer (NSCLC) for daily management of patients and/or for use in research settings.

Over the past decade, several methods to measure skeletal muscle mass in cancer have been investigated, as listed in Table 1 [14–17]. All of these methods are more accurate than routine anthropometric measurements such as weight or body mass index (BMI, which is based solely on weight and height) [18,19]. Whole body MRI is highly accurate, but is impractical in most clinical settings. CT scanning is now well established for measuring muscle mass and is more precise than the others non-MRI methods listed in Table 1. The use of CT for measuring muscle mass offers an excellent opportunity, as CT imaging is routinely utilized in cancer care [20]. Prior studies in healthy volunteers demonstrated that the area determined from a single abdominal slice on MRI correlated closely with total body skeletal muscle (r=0.924) and adipose tissue (r= 0.889). The closest correlation was at the L3 intervertebral space [21,22]. Previously, a strong correlation between MRI and CT imaging had been established using cadaveric thighs (r= 0.999) [23].

Given the demonstration of usefulness of CT scanning as an accurate measure of skeletal muscle mass, several clinical trials have used this method. Based on the MRI results, all of these trials have focused on imaging at L3. While it is understandable that L3 was selected, this level can be problematic for use in patients with lung cancer. At many institutions a chest CT does not always include the third lumbar vertebrae or interspace. In a recent trial in which the majority of patients had lung cancer, only 65% had useful scans for the evaluation of skeletal muscle mass at the L3 level [24]. Future enrollment of lung cancer patients in trials studying sarcopenia, or clinical assessment of patients, would require additional imaging in addition to the chest CT in many patients to assess skeletal muscle index (SMI) at L3. This would increase costs, radiation exposure, and inconvenience. The aforementioned study by Shen et. al., that indicated the closest correlation of total body

skeletal mass with L3 level, also showed an excellent correlation at the L1 level (r = 0.903) for skeletal muscle mass measurement, in normal volunteers [21,22]. A study with small cell lung cancer patients confirmed a strong correlation between L1 and L3 muscle mass index (r=0.8551) [25] and on a similar methodology with head and neck cancer patients, C3 level assessment strongly predicted L3 muscle (r=0.785) [26]. In this study, the objective was to establish that in patients with NSCLC, the L1 level would be included in most chest CT scans and would prove evaluable for patients with advanced cancer. Conditions such as muscle edema, abdominal ascites, and whole body anasarca, can potentially interfere with accurate measurement at any potential lumbar vertebrae level. If it can be established that routine chest CTs in this population can be evaluated for skeletal muscle mass at the L1 level, then such measurement could be practical both for routine patient assessment and in research studies investigating methods to prevent, ameliorate and reverse sarcopenia.

Methods

Patients and study design

All patients included in this trial were required to have non-small cell lung cancer and were about to start a new chemotherapy. Patients' treating oncologists chose the specific cytotoxic chemotherapy regimen. These patients were also part of a prospective, randomized multicenter clinical trial which incorporated the use of a well validated health related quality of life measure, the LCSS [27], which was administered using electronic media every 3 weeks [28]. All patients had stage IIIB or IV biopsy-proven NSCLC, had a Karnofsky performance status of KPS ≥ 60 or Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2, and a life expectancy greater than three months. Enrollees could be receiving first-line, second-line, or third-line chemotherapy (NCT01924416).

Radiological evaluation

Initial CT scans were performed prior to chemotherapy, as a baseline. Repeat CT scans were performed at the discretion of the treating physician. The SMI was determined from these CT scans. The determination of the adequacy of inclusion of the L1 level on the CT was made using a Picture Archiving and Communication System (PACS) workstation with utilization of sagittal reformats when available in assisting precise localization. Contiguous 5-mm Chest CT slices were reviewed. To allow for occasional anatomical variations, if twelve rib pairs were not present (whether greater than or less than twelve), the level below T12 was chosen as the level of interest. The most central slice within the vertebral level was selected and exported into the Slice-O-Matic software® (Tomovision, Magog, Quebec Canada) [29]. This software views and measures the area of interest, using appropriate Hounsfield unit ranges as previously established for skeletal muscle [−29 to150] [20,29]. The abdominal wall, intercostal, and paraspinal muscles, as well as the visualized diaphragmatic crura were tagged. Data pertaining to the selected tissue including the surface area was expressed in squared centimeters (cm^2) by the software. CT chest scan with L1 inclusion and software analysis were performed by trained researchers; with further evaluation and approval by a board certified clinical radiologist.

Outcome measurements

The anthropometric measurements (height and weight) were determined to the closest centimeter and 100 grams. Body mass index (BMI) was calculated and defined for adults. Body surface area was calculated by Dubois formula. Skeletal muscle mass (SMM) assessment is presented as an index - the skeletal muscle index (SMI, measured in cm^2/m^2) - obtained by the skeletal muscle mass cross sectional area (cm^2) at L1 and BSA (m^2). Previously reported cut-off values of SMI (<38.5 cm^2/m^2 for women and <52.4 cm^2/m^2 for men) were used to define sarcopenia [20].

Statistical analysis

Descriptive statistics were summarized by frequency percentages for categorical variables. When normally distributed, data were presented by mean, median, standard deviation and range for continuous variables, with confidence intervals. Correlations were expressed using the Pearson correlation coefficient (r). The coefficient of determination (r^2) was used to calculate the relationship between BMI and SMI.

Results

Patient characteristics

Participants were enrolled from three institutions (Jacobi Medical Center, Montefiore Medical Center, and University of Virginia Medical Center). This analysis evaluated 37 patients who received 73 CT scans including baseline and follow up studies (32 second and 4 third scans after baseline performed at the discretion of the treating physician). Patient demographic and anthropomorphic characteristics are summarized in Table 2. The population was typical for those presenting with advanced lung cancer, with 77% having stage IV disease, a mean age of 62 and with 47% women. The mean Karnofsky PS was 80% and the mean BMI was at the top of the normal range, at 25. The mean weight was 73 kg; only 3% of patients had a low BMI (BMI<18.5), and 15% were characterized as obese with BMI>30.

Adequacy of imaging at L1 for SMI (skeletal muscle index) evaluation

Of the 73 CT scans, 94.5% included L1 (95% CI = 86.6% – 98.5%). Inclusion of L1 differed only slightly among the 3 institutions ranging from 90.4% to 96.7% of CT scans. Additionally, 3 images (4%) were difficult to evaluate due to the following reasons: one patient was too obese for proper imaging, one had poor quality scans and one patient had marked effusions making it difficult to distinguish muscle accurately with the imaging and software.

Detection of Sarcopenia and relationship to BMI and Weight

As seen in Figure 1, sarcopenia was found in 14.7% of all patients; in 34.6% of males (the skeletal muscle index or SMI < 52.4 cm^2/m^2) and in 5.8% of females (SMI < 38. cm^2/m^2) at baseline. In contrast, as seen in Figure 2, there was a weak correlation between BMI and SMI of r= 0.329 at L1 level (with a low coefficient of determination, r^2=0.108). Weight and SMI were not well correlated (r=0.389, r^2=0.151).

Discussion

In this study, Skeletal Muscle Index (SMI) evaluation in routine chest CT scans in patients with lung cancer was practicable at L1 level. This was demonstrated by the fact that 93% of scans from three different institutions had acceptable quality for evaluation. L1 inclusion varied from 90% – 97% given the different radiologic protocols employed at various institutions. These results are superior when compared to prior lung cancer studies reporting L3 level CT image inclusion ranging from 65% to 84% in four prior studies (Prado et al 84% N=275 [30], and Stene et al 84% N=54 [10], Martin et al 70% N=2115 [18], Sun L et al 65% N=140 [24]). Two studies reported unacceptable images in 3.6% and 18% of included patients [10,30], while the current study found the frequency of unacceptable images in 4% due to conditions that were likely to be present at the L3 level as well.

Wasting of skeletal muscle is common in patients with NSCLC, even in those with normal or high body weight or normal BMI, and is associated with poor outcomes, as its severity muscle wasting increases, mortality rates increase as well. In a recent study in patients with NSCLC, sarcopenia was found on 61% of men and in 31% of women at L3 level (N414) [31], independently, our evaluation showed 34% of men had sarcopenia whereas women had a lower of 6% at L1 level. This major results difference is likely due to continuing evolving cut-points. As previously reported, Martin, et. al. proposes a novel and detailed definition of sarcopenia established by a retrospective stratification including cut off values of weight loss >8% and BMI ≥25 cm^2/m^2 [18]. This would then define SMIs at different levels (<53 cm^2/m^2 for males and <41 cm^2/m^2 for females). This newer SMI definition would have included more of the current patients as having sarcopenia. Other authors have adjusted their definitions for sarcopenia according to their populations' skeletal muscle mass and target outcomes [32, 33]. Most recently, Kim EY et. al. estimated a specific L1M1 cut-points for a Korean weight and BMI baseline population to an even lower level for males (<46 cm^2/m^2) and for females (<29 cm^2/m^2), with sensitivity, specificity and accuracy of 98.2, 100 and 98.9 % respectively [25]. Determination of specific cut-points for the L1 level continues to evolve and may be tailored to specific populations in the future.

Selecting the optimum method for assessing body composition using anthropometry depends on the purpose (i.e. evaluating obesity or undernutrition) and requires practitioners to have a good understanding of both practical and theoretical limitations [19]. BMI is not adequate for estimation of muscle mass at either the L3 or the L1 level, as shown in this study with a weak correlation of r= 0.33. This is similar to prior studies at the L3 levels showing the following correlation in various malignancies: a) in NSCLC (r=0.35, in 441 patients) by Baracos et al [31]; b) in SCLC r=0.597 (n=149) by Kim et al [11]; c) in Lung and GI cancers r=0.35 (n=1400) by Martin et al [18]; d) in lymphomas r=0.31 (n=46) by Sarkozy et al [34]; and e) in colorectal cancer r=0.42 9 (n=684) by Prado et al [30]. The coefficient of determination (r^2=0.11) showed that only 11% of the total variation in BMI could be explained by the linear relationship between BMI and SMI while the other 89% of the total variation in BMI remains unexplained. Skeletal muscle mass loss and function may precede overt cachexia, demonstrating the importance of evaluating sarcopenia, rather than weight loss alone. CT images may reveal otherwise occult muscle depletion [9], including reported sarcopenic obesity in 15% of Lung cancer patients [30]. The current study found a

22% rate of sarcopenic obesity in this lung cancer population. On the other hand, an increase in muscle mass during chemotherapy, has been shown to be associated with improved survival [10] but without a correlation with an increase in BMI.

Advanced lung cancer continues to lead in cancer death for both men and women in the U.S. [35], often presenting with muscle loss, impaired physical activity, and diminished quality of life. The early recognition of sarcopenia, often manifesting before decline in weight or BMI, supports evaluation of muscle mass through already obtained CT scans. Such evaluation can reveal sarcopenia earlier than performance status determination as well [36]. The use of CT at L1 is reliable and presents the opportunity for easy patient evaluation of SMI without the need for additional testing or radiation exposure. Utilization of assessment of muscle mass at L1 enhances identification of patients with sarcopenia, and should permit easier evaluation for patients entered into cancer cachexia clinical trials [37], such as those investigating selective androgen receptors [38], gherlin agonist hormones [39], and other new approaches [40–42].

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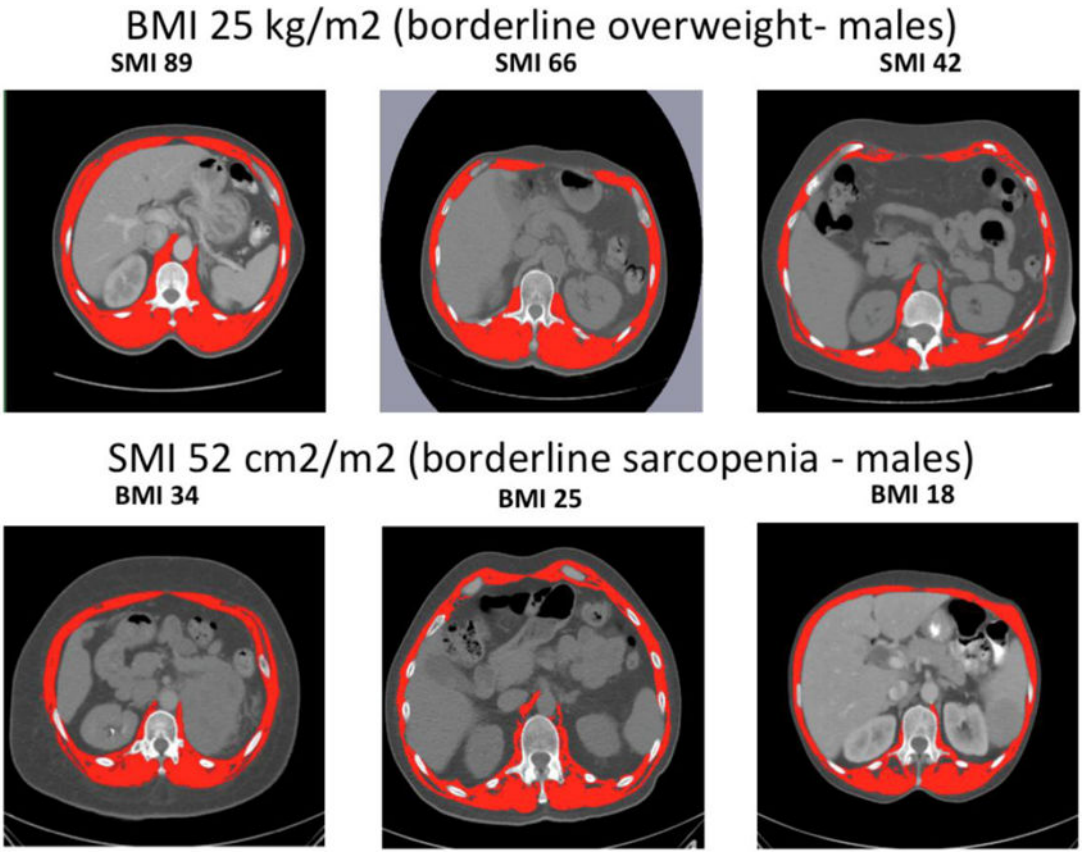

Figure 1. Skeletal Muscle Index at L1 level Computed Tomography Images

Upper row: Difference between patients with BMI 25 kg/m2 (borderline overweight) and different levels of SMI as determined by CT scan. Lower row: Difference between patients with SMI 52 cm2/m2 (borderline sarcopenia - males) and different levels of BMI. Muscle mass tagged in red.

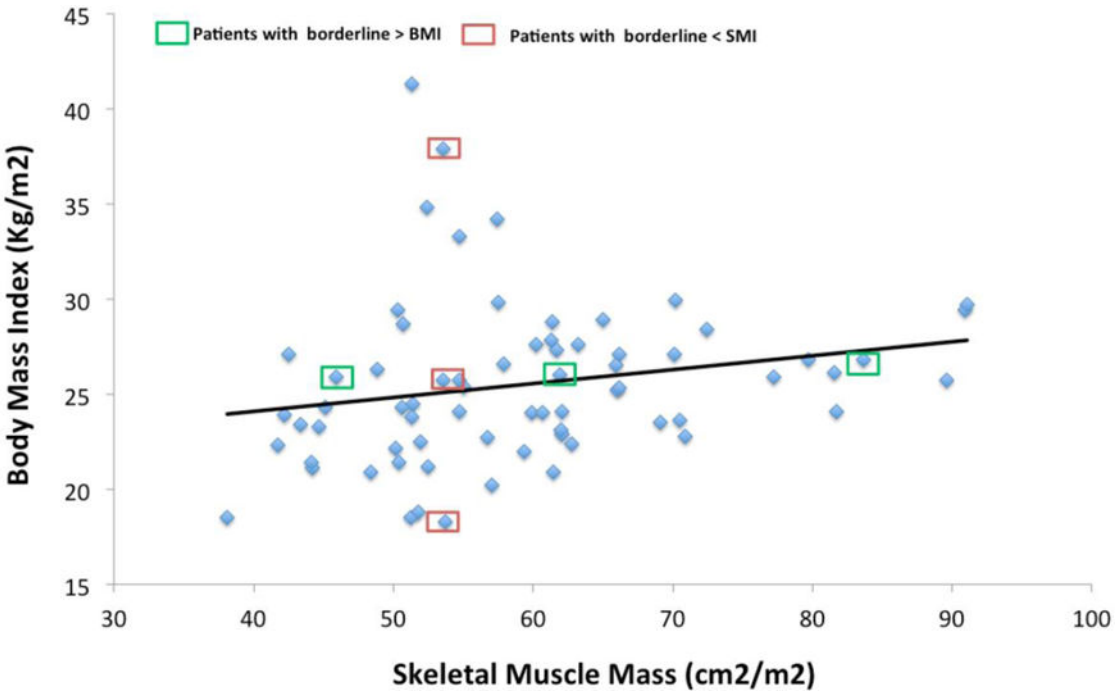

Figure 2.
Correlation of Skeletal Muscle Index at L1 level with Body Mass Index

Table 1

Methods to measure skeletal muscle mass

Tool	Accuracy (SD in kgs)	Advantages	Disadvantages
Bioelectrical impedance (BIA)	9.3	Safe; inexpensive; portable; expedient; no radiation	Relies on population-specific regressions not patient centered; not available at most cancer centers; skeletal muscle quality not evaluated; limited by BMI>34k/m2 that may overestimate muscle mass
Ultrasound (US)	NA	Safe; portable; expedient; low-cost; accessible; reliable for adipose tissue	No standardization technique (anatomical site, position or compression); patient habitus/ hydration limitations and muscle contraction/ relaxation state; operator dependent; provides muscle qualitative rather than quantitative measurements; no studies on cancer patients
Dual X ray absorptiometry (DXA)	3	Low-cost; can add limb muscle to trunk evaluation; low-radiation; better precision and accuracy	Low radiation exposure; cannot discriminate adipose and lean tissue; two-dimensional; influenced by tissue thickness and hydration; skeletal muscle quality not evaluated
Computed Tomography (CT)	<1.2	Clinically routinely accessible; accurately discriminates quantitative and qualitative muscle-fat body composition; high precision and reproducible predicting total LBM, CV=0.13–1.6%	Radiation exposure; dependent on a ‘slice’ at L3 availability; cannot accommodate large individuals in the scanner; presumed strong correlation to MRI not evaluated
Magnetic Resonance Imaging (MRI)	<1	Gold Standard; safe; excellent image quality; L3 level correlates with whole body scan (r: 0.924)	Costly and time consuming; not routinely used; cannot accommodate large individuals in the scanner

Table 2

Patient demographic and anthropomorphic characteristics

Demographics	Value (Range)	SD
Age (median years)	59 (42–84)	11.08
Female/Male (%)	45/55	NA
Stage III/IV (%)	23/77	NA
KPS (%)	80 (50–100)	13.65
Weight (Kgs)	72.97 (45.6–112.9)	13.38
BMI (kg/m2)	25.49 (18.3–41.3)	4.26
SMI (cm2/m2)	59.24 (38.1–91.1)	12.26