Prognostic Significance of CT-Determined Sarcopenia in Patients with Small-Cell Lung Cancer

Eun Young Kim, MD, Young Saing Kim, MD,† Inkeun Park, MD,† Hee Kyung Ahn, MD,† Eun Kyung Cho, MD,† and Yu Mi Jeong, MD**

Introduction: The primary objective of this study was to determine the prognostic significance of computed tomography (CT)-determined sarcopenia in small-cell lung cancer (SCLC) patients.

Methods: This retrospective study consisted of a total of 149 consecutive SCLC patients. The cross-sectional area of muscle at the level of the third lumbar vertebra (L3) was measured using baseline CT images. Sarcopenia was defined as a L3 muscle index of less than 55 cm^2/m^2 for men and of less than 39 cm^2/m^2 for women as proposed by international consensus of cancer cachexia. In addition, Korean-specific cutoffs for sarcopenia was also applied (49 cm^2/m^2 for men and 31 cm^2/m^2 for women). Overall survival (OS) and clinical characteristics of patients with or without sarcopenia were compared.

Results: Mean patient age was 68.6 ± 9.5 years. Most were male (85.3%) and 67.8% had extensive disease at time of diagnosis. Sarcopenia was present in 118 patients (79.2%) and was significantly related to an advanced age ($p = 0.028$), male sex ($p < 0.001$), lower body mass index ($p < 0.001$), and poor performance status ($p = 0.049$). Sarcopenic patients had shorter OS than nonsarcopenic patients (median: 8.6 months versus 16.8 months; $p = 0.031$). Multivariable analysis revealed that sarcopenia was an independent prognostic factor of poor survival (hazards ratio: 1.68; 95% confidence interval: 1.04–2.72; $p = 0.034$), along with extensive stage ($p < 0.001$), supportive care only ($p < 0.001$), and an elevated lactate dehydrogenase level ($p = 0.020$). Using Korean sarcopenia cutoffs, sarcopenic patients were also found to have poorer OS than nonsarcopenic patients, however, the survival difference was not statistically significant (median: 8.4 months versus 12.7 months; $p = 0.144$ by the log-rank test).

Conclusions: Sarcopenia as determined by CT could be used to predict prognosis in patients with SCLC. Optimum reference values to predict cancer-specific outcomes should be tailored by further studies.

Key words: Sarcopenia, Skeletal muscle, Prognosis, Small-cell lung cancer, Tomography, X-ray computed

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Lung cancer is the leading cause of cancer death worldwide and small-cell lung cancer (SCLC) accounts for about 15% of all cases.[1,2] SCLC grows rapidly and most patients present with disseminated disease at the time of diagnosis. Although SCLC is highly responsive to initial chemotherapy and radiotherapy, its prognosis is poor; median survival durations are only 15 to 20 months for limited stage and 8 to 13 months for extensive stage.[3,4]

Clinical outcomes depend not only on tumor-related factors, such as disease extent, but also on host factors, such as performance status (PS) and weight loss.[5] Weight loss, which is a key diagnostic criterion for cancer cachexia, is common at presentation in patients with SCLC. However, it may be misleading sometimes as the evaluation of body weight change depends on patient response during a medical examination.[6] In addition, body weight change does not precisely reflect body composition change, and weight loss is uncertain in patients with a large tumor mass or fluid collection, such as pleural effusion or body edema.

Loss of muscle mass is an important age-related health implication in older persons, and because sarcopenia is a modifiable factor associated with physical disability, injuries, and mortality, it is important that the status of muscle mass be recognized. In addition, the clinical importance of sarcopenia is being increasingly recognized as a component of cancer cachexia syndrome.[7] The prognostic significance of sarcopenia has been revealed for several cancers, such as breast cancer, hepatocellular carcinoma, and advanced urothelial cancer, because the status is associated with functional impairment, increased risk of chemotherapy-related toxicities, and reduced survival.[8–13] Given this increasing recognition, a recent international consensus established sarcopenia as a key diagnostic criterion for cancer cachexia.[14] However, few studies have addressed the prognostic significance of CT-determined sarcopenia in SCLC patients. Accordingly, the primary objective of this study was to determine the prognostic significance of sarcopenia as assessed by baseline CT in SCLC.

*Department of Radiology, and †Division of Hematology and Oncology, Department of Internal Medicine, Gachon University Gil Hospital, Incheon, Republic of Korea.

All authors participated in the concept/design, data interpretation, drafting, and critical revision of the article. The statistical analysis was conducted by Young Saing Kim.

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Address for correspondence: Young Saing Kim, MD, Division of Hematology and Oncology, Department of Internal Medicine, Gachon University Gil Medical Center, 1198 Guwol-dong, Namdong-gu, Incheon 405-760, Republic of Korea. E-mail:zoomboom@hanmail.net

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PATIENTS AND METHODS

Patients

The radiology database and medical records system at Gachon University Gil Medical Center (Incheon, Korea) were searched for patients with newly diagnosed, pathologically proven SCLC that underwent a whole body PET/CT scan from January 2010 to November of 2014.

Height and weight were measured and functional status was recorded at first visit to our oncology department. Body mass index (BMI) was defined as weight divided by height squared (kg/m^2), and BMI values were categorized as underweight (less than 18.5 kg/m^2), normal (18.5–22.9 kg/m^2), overweight (23.0–24.9 kg/m^2), or obese (greater than or equal to 25 kg/m^2).[15]

SCLC was classified using two stages, that is, as limited or extensive. Limited stage was defined as American Joint Committee on Cancer stages I to III, which can be safely treated by definitive radiation therapy.[16] Treatment for SCLC included active therapies, such as chemotherapy, chemoradiotherapy (including sequential and concurrent therapy), chest radiotherapy, and supportive care only. The institutional review board of our hospital approved this retrospective study and waived the requirement for informed patient consent.

PET/CT

All patients fasted for at least 6 hours before PET/CT to ensure a normal blood glucose level. About 60 minutes after the intravenous administration of 370 MBq (10 mCi) of FDG, imaging was performed using an integrated PET/CT device (Siemens Medical Systems, Erlangen, Germany), equipped with lutetium oxyorthosilicate crystal PET detectors, and six slices of CT detectors.

CT imaging was performed from the head to the pelvic floor without contrast administration using the following parameters: 130 kVp, 110 mAs, 2-mm pitch, 1-second tube rotation, and a slice thickness of 5 mm, which matched the section thickness of PET images. Subsequent PET scanning was performed using five to eight table positions for adequate coverage from head to pelvic floor. CT data were used for attenuation correction and PET image data were reconstructed using an ordered set expectation maximization algorithm.

Image Analysis

CT images of whole body PET/CT scans obtained at the time of diagnosis were retrospectively analyzed by a subspecialty-trained chest radiologist. The third lumbar vertebra (L3) was selected as a landmark since the cross-sectional area of tissues in this region provide an established means of estimating total body tissue quantities in the general population. This technique has reported Pearson correlation coefficients ranging from 0.71 to 0.92.[17,18] Two consecutive CT images extending from L3 in the inferior direction were assessed.

Body composition analyses were performed using commercially available software (Terarecon 3.4.2.11, San Mateo, CA). Tissue cross-sectional areas (cm^2) of respective tissues in slices were computed automatically by summing appropriate pixels. The CT Hounsfield unit (HU) ranges used for specific tissues were −29 to 150 HU for skeletal muscle and −190 to −30 HU for adipose tissue. After applying threshold methods using a predefined HU threshold set for each slice, boundaries between different tissues were corrected manually when necessary. L3 muscle index (cm^2/m^2) was defined as the cross-sectional area of muscle at the L3 level normalized for stature as is conventional for BMI.

Definition of Sarcopenia

Sarcopenia was defined as a L3 muscle index of less than 55 cm^2/m^2 for men and of less than 39 cm^2/m^2 for women, as proposed by international consensus of cancer cachexia.[14] In addition, we subsequently analyzed the prevalence and prognostic significance of sarcopenia using Korean-specific cutoffs for sarcopenia. A previous epidemiologic study evaluated height-adjusted appendicular skeletal muscle mass (ASM; kg/m^2) of a young reference group of Koreans using dual energy X-ray absorptiometry (DXA), and determined sarcopenia cutoff values for Korean men and women of 6.58 and 4.59 kg/m^2, respectively.[19] A previous study[18] showed that L3 muscle area by CT and ASM by DXA are linearly related by the regression equation:

$$\text{L3 muscle index}\left(\text{cm}^2/\text{m}^2\right) = \left[\text{height-adjusted ASM}\left(\text{kg}/\text{m}^2\right) - 1.17\right]/0.11$$

We used this equation to calculate corresponding L3 muscle index cutoff values of 49 cm^2/m^2 for men and 31 cm^2/m^2 for women.

Statistical Analysis

Descriptive statistics are reported as proportions or means with standard deviations. For categorical variables, comparisons between subjects with and without sarcopenia were performed using Pearson's χ^2 test or Fisher's exact test. Continuous variables were compared using the Student's *t* test or the Mann–Whitney *U* test. Survivals were estimated using the Kaplan–Meier method and survivals were compared using the log-rank test. Overall survival (OS) was estimated from date of baseline PET/CT to death or last follow-up. Univariable and multivariable Cox proportional hazard models were used to identify prognostic factors of survival. Variables with a *p* value of less than 0.15 by the log-rank test were included in the multivariable analysis. Two-sided *p* values of less than 0.05 were considered statistically significant. The analysis was performed using SPSS for Windows ver. 19.0 (SPSS Inc., Chicago, IL).

RESULTS

Characteristics of the Study Population

A total of 149 consecutive patients were included in this study (Table 1). Mean patient age was 68.6 ± 9.5 years and 127 (85.2%) were male. Of the 149 patients, 101 (67.8%) had extensive disease at first presentation, and 31 patients (20.8%) received supportive care only. Average BMI was 22.1 ± 3.5 kg/m^2 and 16.1% of the patients were underweight