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Clinical implications of sarcopenia in patients undergoing complete resection for early non-small cell lung cancer

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ABSTRACT

Objectives: Sarcopenia is characterized by progressive and generalized loss of skeletal muscle mass and strength. We aimed to investigate sarcopenia in patients with stage I non-small cell lung cancer (NSCLC) who underwent complete resection, and the relationship of sarcopenia with clinicopathological factors.
Methods: All consecutive patients who underwent lung resection between January 2005 and December 2008 were enrolled in this retrospective study. Eligible patients were assigned to one of 2 groups according to the presence or absence of sarcopenia, as assessed by the sum of cross-sectional areas of skeletal muscles in the region of the third lumbar vertebra (L3) on preoperative computed tomography (CT).
Results: Sixteen of 52 male (30.8%) and 22 of 38 female (57.9%) patients were identified with sarcopenia ($p = 0.01$). Patients with sarcopenia were more likely to have a low body mass index (BMI) ($p < 0.0001$). Kaplan-Meier analysis showed that patients with sarcopenia had a significantly worse outcome than patients without sarcopenia (5-year-survival: 72.8% vs 85.8%, respectively, $p = 0.028$). Multivariate analysis found that sarcopenia was a significant independent prognostic factor (hazard ratio: 7.09, $p = 0.0008$).
Conclusions: Sarcopenia identified on a cross-sectional CT image of the L3 level was associated with poor outcome with completely resected early-stage NSCLC.

1. Introduction

Lung cancer is the leading cause of cancer death in most countries. Surgery is the best therapeutic modality for achieving a cure for patients with early-stage lung cancer. However, the outcome of patients with non-small cell lung cancer (NSCLC) who undergo complete resection has been reported to be worse than the outcome of patients with other definitively treated early-stage cancers; the 5-year postoperative survival rate of patients with stage IA NSCLC has ranged from 73% to 82%, which indicates that recurrent disease developed in more than 20% to 30% of stage IA patients [1,2].

Prognostic information on patients with early stage NSCLC who will undergo surgical resection is important for deciding on follow-up methods or on whether to administer postoperative adjuvant treatment. Many prognostic factors have been investigated for lung cancer patients, and many disease-related factors have been identified, including pathological stage (tumor size, tumor invasion, and lymph node metastases). However, factors related to the physical status of a patient have also been reported to be important predictors of postoperative outcomes.

Among the parameters of physical status, the performance status (PS) and smoking history are well validated factors that are associated with the postoperative outcomes of patients with early-stage lung cancer, as well as the outcomes of patients with advanced-stage lung cancer [3]. In addition, the nutritional status of a patient has been reported to be an important predictor of postoperative fitness. Poor nutritional status is associated with a low activity-of-daily-living (ADL) score, which may impair patient compliance with anticancer treatment, consequently resulting in unfavorable postoperative survival. Recent studies have shown that a lung cancer patient's body status, including low body weight and low body mass index (BMI), predicts unfavorable surgical outcomes for both survival and postoperative morbidities [4,5].

Sarcopenia is a syndrome that is characterized by progressive and generalized loss of skeletal muscle mass and strength. It carries a risk of adverse outcomes such as physical disability, poor

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quality of life, and mortality [6]. Sarcopenia was first evaluated to predict the treatment outcomes associated with functional impairment in patients with geriatric syndrome. Several recent studies have shown that sarcopenia has prognostic significance for surgical and nonsurgical patients with malignant disease, including cancers of the esophagus, colon, pancreas, liver, urinary tract, and female reproductive tract. The impact of sarcopenia on the surgical outcomes of patients with lung cancer has not been reported. We therefore investigated sarcopenia in patients with stage I NSCLC who underwent complete resection. To determine the clinical implications of sarcopenia in patients with early-stage lung cancer, we assessed the relationship of sarcopenia with clinicopathological factors.

2. Materials and methods

2.1. Patients

All consecutive patients (n = 137) who underwent lung resection with curative intent as the initial treatment in the Department of Surgery II, Kyushu University Hospital, between January 2005 and December 2008, were enrolled in this retrospective study. Among those patients, a total of 90 patients whose CT scans were available for assessment at the L3 level were finally investigated. Curative resection was defined as complete macroscopic removal of the tumor. All patients underwent preoperative computed tomography (CT). Images were analyzed using OsiriX, version 5.8 software (Pixmeo, Bernex, Switzerland). Sarcopenia assessment was performed on each patient's scan by evaluating a transverse CT image of the region at the third lumbar vertebra (L3) in the inferior direction.

The histopathological diagnosis of the tumor was based on the World Health Organization histological classification of lung tumors [7]. Pathological staging was determined using the seventh edition of the TNM classification system of the Union for International Cancer Control (UICC) [8].

2.2. Calculation of skeletal muscle mass

Skeletal muscle was identified based on Hounsfield unit (HU) thresholds of −29 to +150 (water is defined as 0 HU, air as 1000 HU) [9]. The following muscles in the L3 region were assessed: psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and the rectus abdominis (Fig. 1). The cross-sectional areas (cm^2) of these muscles were computed automatically by adding together a given tissue's pixels and multiplying by pixel surface area. Intraperitoneal organs and spinal cords were manually excluded. The cross-sectional areas were then normalized for height (cm^2/m^2). Cut-off values for skeletal muscle were defined in accordance with a previous report as 43.75 cm^2/m^2 for men and 41.10 cm^2/m^2 for women [10]. Based on this cut-off, patients were assigned to one of 2 groups, according to the presence or absence of sarcopenia. The clinicopathological background and rates of overall and recurrence-free survival of the patients with and without sarcopenia were compared.

The following candidate predictive factors were examined with respect to overall and recurrence-free survival: sarcopenia (presence versus absence); age (<70 versus ≥70 years); gender (male versus female); body mass index (BMI); performance status (0 versus 1); TNM stage (IA versus IB); tumor differentiation (well differentiated + moderately differentiated versus poorly differentiated); surgical procedure (partial resection + segmental resection versus lobectomy + bilobectomy + pneumonectomy); and anemia (presence versus absence). Anemia was defined as a hemoglobin level <13.7 g/dL for males and <11.6 g/dL for females, according to the cut-off level of the hospital's laboratory. We also investigated each patient's comorbidities, serum albumin, and C-reactive protein (CRP) levels to assess nutritional status and inflammatory burden.

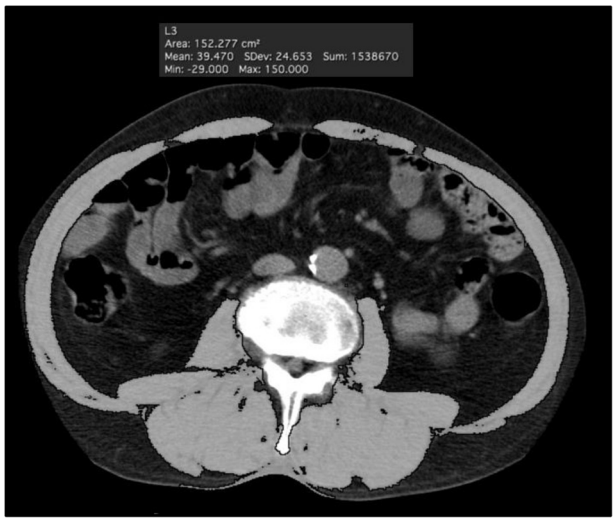

Fig. 1. Computed tomography image showing areas (light gray) of skeletal muscle in the region of the third lumbar vertebra.

2.3. Operative morbidity

Postoperative complications occurring within 1 month after lung resection included bleeding, prolonged air leakage, bronchopleural fistula, pleural effusion, atelectasis, pneumonia, and surgical site infection.

2.4. Patient follow-up

After discharge, all patients were examined monthly for recurrence by conventional chest radiography and assessment of tumor markers (CEA, CYFRA) and every 6 months by CT. When recurrence was suspected, additional examinations were performed, including positron emission tomography and magnetic resonance imaging of the head. Recurrent lung cancer was treated by chemotherapy and/or radiation therapy.

Disease-free survival (DFS) was defined as the time after surgery to the diagnosis of recurrence or until death from any cause. Overall survival (OS) was defined as the time after surgery to death from any cause. Our institutional review board approved this retrospective study (Kyushu University, IRB No.27-241).

2.5. Statistical analysis

The association of continuous and categorical variables with relevant outcome variables was assessed using the Mann-Whitney *U* test and Fisher exact test, respectively. To identify prognostic factors after lung resection, all variables were included in the overall multivariable Cox proportional hazards model for the analysis of OS and DFS, using the backward selection method. OS and DFS curves were created using the Kaplan-Meier method, and the curves were compared using the log-rank test. All analyses were performed using JMP Pro, version 11.0.0 software (SAS Institute Inc., CARY, North Carolina, USA). $P < 0.050$ was considered statistically significant.