Sarcopenia Evaluated Using the Skeletal Muscle Index Is a Significant Prognostic Factor for Metastatic Urothelial Carcinoma

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Abstract

The prognostic significance of sarcopenia (muscle loss) in patients with metastatic urothelial carcinoma (UC) is unclear. Furthermore, its evaluation methods are not entirely standardized. Using several types of computed tomography-based evaluation, we assessed the association of sarcopenia with survival in patients with metastatic UC. Multivariate analysis showed that sarcopenia was an independent prognostic factor in an evaluation using skeletal muscle index.

Background: The purpose of the study was to evaluate the prognostic value of sarcopenia (muscle loss) in patients with metastatic urothelial carcinoma (UC), in a comparison of several methods of computed tomography (CT)-based evaluation of sarcopenia. **Patients and Methods:** We retrospectively reviewed 100 patients with metastatic UC who underwent first-line systemic chemotherapy between 2003 and 2014. Sarcopenia was assessed by the following CT-based methods: skeletal muscle index (SMI), total psoas area (TPA), axial and/or transversal psoas thickness at the level of the third lumbar vertebrae, and axial and/or transversal psoas thickness at the umbilicus level (U-TPT). All parameters were standardized by either height or height squared. Cutoff points were SMI: < 55 cm^2/m^2 (men), < 39 cm^2/m^2 (women); others: lowest sex-specific quartiles. Predictive values for cancer-specific survival (CSS) were assessed using the Cox proportional hazards regression model. **Results:** Sixty-four patients met the eligibility criterion for analysis: those who underwent CT scans within 30 days before chemotherapy. Of them, 52 (81%) died of UC during the follow-up, with a median survival time of 13 months. Univariate analysis associated decreased SMI, TPA, and U-TPT with poor CSS. Multivariate analysis together with other pretreatment clinicopathologic parameters showed decreased SMI to be an independent predictor of poor CSS. **Conclusion:** Evaluation using SMI showed sarcopenia was an independent predictor of poor prognosis for patients with metastatic UC who underwent first-line systemic chemotherapy. Our results might improve stratification of patients and help optimize evaluation of sarcopenia.

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Introduction

In 2012, approximately 430,000 patients were diagnosed with urothelial carcinoma (UC) of urinary bladder, resulting in 160,000 deaths worldwide.[1] Metastatic UC is known to be intractable, with a median survival of 14 months, even after implementation of contemporary cisplatin-based chemotherapy regimens.[2,3]

Although sarcopenia (age-associated loss of skeletal muscle mass[4]), is reportedly associated with adverse outcomes in many malignancies,[5-14] to our knowledge, no study has been conducted to investigate its prognostic significance in metastatic UC, despite recent reports associating sarcopenia with outcomes of surgery for localized bladder cancer.[12-14]

Moreover, evaluation methods for sarcopenia are not entirely standardized. Although a recent European consensus definition of sarcopenia described computed tomography (CT) and magnetic resonance imaging as gold standards for estimating muscle mass in research,[15] several possible alternatives exist. We thus compared

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several evaluation methods for sarcopenia with special regard to its prognostic values in metastatic UC patients.

Patients and Methods

Patients

Institutional review board approval was obtained for the study. We reviewed 100 patients with metastatic UC who received first-line systemic chemotherapy at our institution between April 2003 and February 2014. This cohort included 83 patients who were analyzed in our previous study on general prognostic markers.[16] Because axial CT images obtained within 30 days before the baseline evaluation were reported to accurately represent muscle status and were recommended for analysis of sarcopenia,[17] we excluded 36 patients who did not undergo pretreatment CT within 30 days of chemotherapy, leaving 64 available for analysis. The median time between the date of the scan and the date of the start of first-line chemotherapy was 9.5 days (interquartile range [IQR], 3-17 days). All patients underwent routine blood tests, chest x-rays and CT scans every 1-6 months. Follow-up information was obtained as of July 2014.

Imaging

For each patient, a radiologist (N.A.) identified the single axial image at the level of the third lumbar vertebrae (L3) on which both transverse processes were fully observed, and the one at the level of the umbilicus. On the basis of these images, the following 6 parameters were calculated for each patient: skeletal muscle index (SMI; cross-sectional area of all skeletal muscles at the L3 level); total psoas area (TPA; cross-sectional area of bilateral psoas muscles at the L3 level); axial and/or transversal psoas thickness at the L3 level (L3-APT and/or L3-TPT); axial and/or transversal psoas thickness at the umbilicus level (U-APT/U-TPT). SMI and TPA were measured using the attenuation thresholds of −29 to 150 Hounsfield units,[18] to remove the "marbling part" of muscles. They were then normalized by height squared and reported as cm^2/m^2 for SMI and as mm^2/m^2 for TPA. According to a previous report,[19] all psoas muscle thicknesses were measured on the right psoas muscle as follows: the largest diameter of psoas muscle for axial psoas thicknesses, and the diameter of psoas muscle perpendicular to the axial diameter for transversal psoas thicknesses. They were then normalized by height and reported as mm/m. All image analyses were performed by a radiologist (N.A.) who was blinded to patient outcomes, using OsiriX version 4.1 (Pixmeo, Bernex, Geneva, Switzerland). Figure 1 shows how the 6 parameters were measured on representative axial CT images at the L3 and umbilicus levels of the same patient.

Statistical Analysis

Cutoff values for SMI were based on international consensus definitions, determined by 2 standard deviations below the norm for young healthy adults (< 55 cm^2/m^2 for men and < 39 cm^2/m^2 for women).[20] Other cutoff values were set at the lowest sex-specific quartiles according to previous studies.[10,11] Spearman rank correlation coefficient was used to evaluate correlations between parameters.

Associations between sarcopenia and other pretreatment clinicopathologic factors with cancer-specific survival (CSS) from the start of first-line chemotherapy were analyzed using Kaplan−Meier curves and compared using log rank tests. Backward stepwise multivariate Cox proportion analysis was performed to determine the influence of each parameter on patients' CSS. Estimated glomerular filtration rate was calculated using the revised formula

Figure 1 Pretreatment Computed Tomography Scans of 1 Patient Show Measurement of (A) Skeletal Muscle Index, (B) Total Psoas Area, (C) L3-Level Axial and/or Transversal Psoas Thicknesses, and (D) Umbilicus-Level Axial and/or Transversal Psoas Thickness