

Decreased Skeletal Muscle Mass is Associated with an Increased Risk of Mortality after Radical Nephrectomy for Localized Renal Cell Cancer

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Abbreviations and Acronyms

ACM = all cause mortality
BMI = body mass index
CSM = cancer specific mortality
CSS = cancer specific survival
CT = computerized tomography
ECOG = Eastern Cooperative Oncology Group
eGFR = estimated glomerular filtration rate
mRCC = metastatic renal cell carcinoma
OS = overall survival
PFS = progression-free survival
RCC = renal cell carcinoma
SMI = skeletal muscle index

Purpose: We evaluate the association between severe skeletal muscle deficiency or sarcopenia, and disease progression, cancer specific mortality and all cause mortality in patients with localized renal cell carcinoma treated with radical nephrectomy.

Materials and Methods: The baseline lumbar skeletal muscle index of 387 patients treated with radical nephrectomy for nonmetastatic renal cell carcinoma between 2000 and 2010 was measured on preoperative computerized tomography. Sarcopenia was classified according to gender specific consensus definitions as male—skeletal muscle index less than 55 cm²/m² and female—skeletal muscle index less than 39 cm²/m². Progression-free, cancer specific and overall survival was estimated with the Kaplan-Meier method. Associations with progression, cancer specific mortality and all cause mortality were summarized with hazard ratios.

Results: Of 387 patients 180 (47%) had sarcopenia. Patients with sarcopenia were older, more likely to be male (77% vs 56%, p < 0.001), to have a smoking history (67% vs 55%, p = 0.02), and to have nuclear grade 3 or greater disease (67% vs 60%, p = 0.05), but were otherwise similar to patients without sarcopenia. Median postoperative followup was 7.2 years. Patients with sarcopenia had inferior 5-year cancer specific survival (79% vs 85%, p = 0.05) compared to those without sarcopenia, as well as significantly worse 5-year overall survival (65% vs 74%, p = 0.005). As a continuous variable, increasing skeletal muscle index was linearly associated with a decreased risk of cancer specific mortality and all cause mortality. Moreover, on multivariable analysis sarcopenia was

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associated with increased cancer specific mortality (HR 1.70, $p=0.047$) and all cause mortality (HR 1.48, $p=0.039$).

Conclusions: Sarcopenia is independently associated with cancer specific mortality and all cause mortality after radical nephrectomy for renal cell carcinoma. These findings underscore the importance of assessing skeletal muscle index for risk stratification, patient counseling and treatment planning.

Key Words: sarcopenia; carcinoma, renal cell; body mass index; nephrectomy; survival rate

OBESITY, as characterized by body mass index, is a well described risk factor for renal cell carcinoma,^{1,2} but has been paradoxically associated with a decreased risk of cancer specific and all cause mortality.^{3,4} However, recent studies that have explored the impact of the precise characterization of body composition through partition of total body mass into lean muscle and adipose compartments have demonstrated that BMI is inadequate and nonspecific in its ability to characterize actual excess adipose tissue vs robust lean muscle mass.⁵⁻⁷ Furthermore, it may obscure the diagnosis of severe lean muscle deficiency, or sarcopenia. Sarcopenia can be associated with adverse outcomes of multiple malignancies, including melanoma, breast, pancreatic, colorectal and hepatobiliary cancer, and urothelial carcinoma of the bladder.^{6,8-11} Furthermore, among patients with metastatic RCC depleted lean muscle stores have been linked to increased sorafenib and sunitinib associated toxicity¹²⁻¹⁵ but not to decreased survival among patients receiving targeted therapies.¹⁶

However, to date the impact of low preoperative skeletal muscle mass has yet to be evaluated as a prognostic feature in patients with clinically localized RCC undergoing radical nephrectomy. Therefore, in this study we assess the impact of lean muscle mass, as quantified on standard preoperative CT, on the risk of disease progression, CSM and ACM in a contemporary cohort of patients with nonmetastatic RCC treated with radical nephrectomy. We hypothesized that decreased lean muscle mass in patients with localized RCC treated with radical nephrectomy would be associated with an increased risk of adverse oncologic outcomes.

PATIENTS AND METHODS

Cohort Selection

After institutional review board approval we identified 1,081 patients treated with open or laparoscopic radical nephrectomy for sporadic, unilateral RCC between 2000 and 2010 from the Mayo Clinic nephrectomy registry. Exclusion criteria were missing digitized axial CT of the abdomen/pelvis within 30 days of surgery as axial imaging within 30 days of surgery has previously been demonstrated to accurately represent muscle status at the time of surgery (626),⁶ evidence of metastatic disease at the time of surgery (233), or missing BMI (3). Some patients may have met more than 1 exclusion criterion.

The final study cohort included 387 patients. To assess for potential bias introduced by the missing data, clinicopathological features were compared between patients who did vs did not have preoperative imaging available for body composition analysis.

Clinical Covariates

Clinicopathological features compared between sarcopenic and nonsarcopenic cases included year of surgery, age at surgery, gender, symptoms, smoking status, ECOG performance status, Charlson score, eGFR (ml/minute/1.73 m²) calculated using the Chronic Kidney Disease Epidemiology Collaboration formula, neoadjuvant treatment and surgical technique, as well as the presence of preoperative symptoms. All pathological specimens were rereviewed by 1 study pathologist (JCC) for histological subtype, tumor size (cm), pathological tumor and lymph node stage, nuclear grade, coagulative tumor necrosis and sarcomatoid differentiation.

Body Composition Analysis

The cross-sectional areas of the lumbar skeletal muscle complement (including the rectus abdominus, and bilateral internal, external and lateral obliques, psoas, quadratus lumborum and erector spinae) were identified using attenuation thresholds of -29 to +150 HU using Slice-O-Matic software (version 5.0, TomoVision, Quebec, Canada) by 1 investigator (SPP).^{17,18} All images were evaluated at a standard skeletal landmark according to previously described methodology (fig. 1).¹⁹

The lumbar skeletal muscle index was calculated by normalizing the lumbar skeletal muscle area by height (m) squared and reported as cm²/m². SMI was assessed as a continuous variable. Patients were also categorized as sarcopenic according to international gender specific consensus definitions, which are based on SMI 2 standard deviations or less below the mean for healthy young adults (age 20 to 40), with male SMI less than 55 cm²/m² and female SMI less than 39 cm²/m².²⁰ Body mass was also described using BMI (kg/m²) as a continuous variable, and categorized as obese or not obese according to WHO criteria (BMI 30 kg/m² or greater).²¹

Patient Outcome

Outcomes of interest included PFS, CSS and OS. Disease status for patients in the nephrectomy registry is updated annually as assessed by patient visit or by mailed questionnaire to the patient and his or her local physician. Cause of death is verified via death certificate.

Statistical Methods

Continuous features were summarized with medians, interquartile ranges and ranges. Categorical features were summarized with frequency counts and percentages.

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