Sarcopenia as a Predictor of Complications and Survival Following Radical Cystectomy

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Abbreviations and Acronyms

ASA® = American Society of Anesthesiologists®

CT = computerized tomography

ICU = intensive care unit

LOS = length of stay

TPA = total psoas muscle area

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Purpose: Patients undergoing radical cystectomy face substantial but highly variable risks of major complications. Risk stratification may be enhanced by objective measures such as sarcopenia. Sarcopenia (loss of skeletal muscle mass) has emerged as a novel biomarker associated with adverse outcomes in many clinical contexts relevant to cystectomy. Based on these data we hypothesized that sarcopenia would be associated with increased 30-day major complications and mortality after radical cystectomy for bladder cancer.

Materials and Methods: We performed a retrospective study of patients treated with radical cystectomy at our institution from 2008 to 2011. Sarcopenia was assessed by measuring cross-sectional area of the psoas muscle (total psoas area) on preoperative computerized tomography. Cutoff points were developed and evaluated using ROC curves to determine predictive ability in men and women for outcomes of major complications and survival.

Results: Of 224 patients with bladder cancer 200 underwent preoperative computerized tomography within 1 month of surgery. Total psoas area was calculated with a mean score of 712 and 571 cm^2/m^2 in men and women, respectively. A clear association was noted between major complications and lower total psoas area in women using a cutoff of 523 cm^2/m^2 to define sarcopenia (AUC 0.70). Sarcopenia was not significantly associated with complications in men. There was a nonsignificant trend of sarcopenia with worse 2-year survival.

Conclusions: Sarcopenia in women was a predictor of major complications after radical cystectomy. Further research confirming sarcopenia as a useful predictor of complications would support the development of targeted interventions to mitigate the untoward effects of sarcopenia before cancer surgery.

Key Words: urinary bladder neoplasms, cystectomy, sarcopenia, postoperative complications, prognosis

ALTHOUGH radical cystectomy is the reference standard treatment for high risk bladder cancer, the potential risks associated with this option have become increasingly salient. Postoperative morbidity and mortality are increasingly recognized as significant concerns with complication rates ranging from 40% to 75%.[1–3] Identifying novel, patient specific

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risk factors for complications may potentially inform treatment decision making and perioperative care. Historical predictive strategies rely on general measures such as ASA classification, body mass index and basic laboratory values.[4,5] The use of such measures has met with limited success for predicting postoperative outcomes, highlighting the need for innovative approaches to risk assessment.

Sarcopenia, defined as degenerative loss of skeletal muscle mass associated with aging and considered a component of frailty,[6] represents a potentially promising risk marker. Although sarcopenia has no standardized definition, the clinical usefulness of objectively measured muscle mass depletion was reported in clinical oncology and major surgery cases.[7–13] Sarcopenia has been measured by various methods with abdominal CT preferred in the surgical oncology setting since it is easily available as part of an oncology evaluation.[10]

By measuring cross-sectional area of the psoas muscle on imaging an objective measure of sarcopenia may serve as a predictive tool for surgeons since most patients scheduled for cystectomy undergo abdominal CT preoperatively. Outcomes using this measure were assessed in 4 surgical studies to date evaluating hepatectomy, pancreatectomy, colorectal surgery and liver transplantation, respectively.[12–15] In each study sarcopenia was a significant independent predictor of postoperative complications.

Drawing from these studies we hypothesized that sarcopenia (defined as decreased psoas muscle area) would be associated with increased 30-day complications and mortality after radical cystectomy for bladder cancer. Since to our knowledge no validated preexisting cutoff points exist, we evaluated specific scores that would lead to the prediction of complications and mortality after cystectomy, thus, objectively defining sarcopenia in this clinical context. As a secondary hypothesis, we also suspected that patients with sarcopenia would experience longer LOS and additional days in the ICU than those without sarcopenia.

METHODS

Patients and Data Collection

We performed a retrospective study by identifying patients in our institutional Genitourinary OncoLogy Database who underwent radical cystectomy for bladder cancer between 2008 and 2011. Patients with available postoperative data and abdominal CT within 30 days of the surgery date were included in analysis. We categorized 30-day complications according to the Clavien score using the Memorial Sloan-Kettering Cancer Center complication grading scheme.[16] Major complications were defined as grade 3 or higher. Days in the ICU and hospital LOS were also recorded to assess their association with sarcopenia status. Mortality data were obtained by chart review and confirmed using the Social Security Death Index. The University of North Carolina institutional review board approved this study.

Image Analysis

Muscle area was assessed by measuring cross-sectional area of the right and left psoas muscles (TPA) on CT using 3-dimensional computerized image analysis (Aquarius® iNtuition™ 4.4). Images were processed and analyzed by a single radiologist. According to prior studies TPA was measured from the craniocaudal direction at the L3 level on the first image with the 2 transverse processes visible.[17,18] Measurements were made in semiautomated fashion with manual outlining of psoas muscle borders and volumetric analysis of the outlined area by setting a density threshold of between −30 and 110 HU. Psoas muscle area was automatically calculated by excluding vasculature, bony structure and areas of intramuscular fatty infiltration based on HU. Measured psoas area was then normalized to patient height in m^2 according to the convention for body composition measurements (TPA in cm^2/m^2).

Statistical Analysis

We used the t-test to evaluate differences in continuous variables between groups and the Fisher exact test for categorical variables. Logistic regression was done to explore the association of other possible predictors of outcomes, including age, gender and ASA score, with the ordered outcome of no complication vs a minor or major complication. The Kaplan-Meier method was used to evaluate the association of sarcopenia with 2-year overall survival as defined by time since surgery.

Notably, in prior sensitivity analysis using TPA as a measure of sarcopenia state in obese individuals with sarcopenia cutoffs of 385 cm^2/m^2 or less in women and 524 cm^2/m^2 in men were proposed.[11] However, because these criteria were developed in populations with different underlying clinical problems (obesity), we performed ROC curve analysis using our data set. We used the ROC AUC (average biomarker sensitivity over the range of specificities), which is often applied as a summary statistic representing overall biomarker performance.[19] The Youden index was then used to determine which cutoff yielded the best combination of sensitivity and specificity.[20]

Also, since most prior studies suggest that there are different sarcopenia thresholds in men and women due to gender specific differences in body composition, we stratified our analysis accordingly.[10] Sensitivity analysis was done to evaluate whether previously used cutoff points had predictive ability. All statistical tests were 2-sided and all analysis was performed with SAS®, version 9.3 with $\alpha < 0.05$ considered statistically significant.

RESULTS

We identified 224 patients with muscle invasive bladder cancer between 2008 and 2011, of whom 24 did not undergo staging CT within 1 month of