Mortality after Radical Cystectomy: Impact of Obesity Versus Adiposity after Adjusting for Skeletal Muscle Wasting

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Purpose: We assess the impact of obesity, as measured conventionally by body mass index vs excess adiposity as measured by fat mass index, on mortality after radical cystectomy for bladder cancer, adjusting for the presence of skeletal muscle wasting.

Materials and Methods: This retrospective cohort study included 262 patients treated with radical cystectomy for bladder cancer between 2000 and 2008 at the Mayo Clinic. Lumbar skeletal muscle and adipose compartment areas were measured on preoperative imaging. Overall survival was compared according to gender specific consensus fat mass index and skeletal muscle index thresholds as well as conventional body mass index based criteria. Predictors of all cause mortality were assessed by multivariable modeling.

Results: Increasing body mass index correlated with improved overall survival (p=0.03) while fat mass index based obesity did not (p=0.08). After stratification by sarcopenia, no obesity related 5-year overall survival benefit was observed (68% vs 51.4%, p=0.2 obese vs normal and 40% vs 37.4%, p=0.7 sarcopenia vs sarcopenic/obese). On multivariable analysis class I obesity according to body mass index (HR 0.79, p=0.33) or fat mass index criteria (HR 0.85, p=0.45) was not independently associated with all cause mortality after adjusting for sarcopenia (HR 1.7, p=0.01) as well as age, performance status, pTN stage and smoking status. However, in patients with normal lean muscle mass each 1 kg/m^2 increase in weight or adipose mass was associated with a 7% to 14% decrease in all cause mortality.

Conclusions: After adjusting for lean muscle wasting, neither measurements of obesity nor adiposity were significantly associated with all cause mortality in patients treated with radical cystectomy, although subanalyses suggest a potential benefit among those with normal lean muscle mass.

Key Words: sarcopenia, obesity, mortality, cystectomy, body mass index

Abbreviations and Acronyms

ACM = all cause mortality
BMI = body mass index
CT = computerized tomography
ECOG = Eastern Cooperative Oncology Group
FM = fat mass
FMI = fat mass index
NHANES = National Health and Nutrition Examination Survey
OS = overall survival
RC = radical cystectomy
SMI = skeletal muscle index

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WORLDWIDE approximately 1.1 billion adults are estimated to be overweight and an additional 475 million are obese. Despite the substantial adverse health outcomes associated with obesity,[1] there is a growing body of literature suggesting that overweight and obese surgical patients have decreased all cause mortality compared to leaner patients.[2] This counterintuitive finding has been coined "the obesity paradox"[3,4] but

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has yet to be described among patients treated with radical cystectomy, in whom the impact of obesity remains unclear.[5–8]

It was estimated that in the United States approximately 75,000 patients would be diagnosed with urothelial carcinoma of the bladder in 2014,[9] of whom approximately 75% were overweight or obese,[6] and for whom the standard of care is neoadjuvant chemotherapy followed by radical cystectomy with bilateral pelvic lymph node dissection and urinary diversion. Unfortunately, even in contemporary series the combined surgical and disease morbidity results in 5-year overall survival rates of only 42% to 58%.[10,11]

In a recent study of a contemporary radical cystectomy cohort we observed a significant risk of increased mortality in patients with sarcopenia, or severe skeletal muscle wasting.[12] We also observed an inverse trend, consistent with the obesity paradox, toward decreased mortality with increasing BMI on unadjusted analysis. However, after adjusting for tumor specific factors, comorbidity and skeletal muscle wasting, BMI was no longer independently associated with all cause mortality.

We hypothesize that our previous findings were related to the nonspecificity of BMI as a measure of body composition, such that patients with a low BMI were likely those who also had skeletal muscle wasting, which strongly predicts poor outcomes in patients with cancer.[12] Thus, we explored the association between obesity as classified by BMI vs FMI, a measure of adiposity and overall survival after RC, adjusting for the presence of lean muscle wasting.

METHODS

Patient Selection

After institutional review board approval we retrospectively identified 515 consecutive patients treated with RC and urinary diversion between 2000 and 2008. Patients were excluded from analysis if preoperative digital imaging was not available within 30 days of surgery (244) or if image analysis was precluded by poor image quality (9), leaving 262 patients (225 men and 37 women) available for analysis.[13,14]

Body Composition Analysis

A representative axial image at the level of L3 was identified by one of 2 radiologists (GDS, MRM). Then cross-sectional skeletal muscle and adipose areas were measured according to attenuation thresholds using SliceOmatic software (v.5.0, Tomovision, Quebec, Canada) by 1 investigator (SPP) who was blinded to patient outcome. Skeletal muscle area was identified using an attenuation threshold of −29 to +150 HU.[12,15] SMI was calculated by normalizing the total skeletal muscle area by height squared (cm^2/m^2).[16] Patients were classified as sarcopenic according to gender specific international consensus reference values, which represent muscularity below the fifth percentile for healthy young adults (male—SMI less than 55 cm^2/m^2, female—SMI less than 39 cm^2/m^2).[14]

Total adipose tissue area includes the total cross-sectional area of all visceral (−150 to −50 HU), intramuscular and subcutaneous adipose tissue (−190 to −30 HU, cm^2) on the L3 axial CT image.[13] Whole body FM (kg) was then calculated using the equation,

$$\text{FM (kg)} = 0.042 \times (\text{total adipose area at L3 in cm}^2) + 11.2^{16}$$

FMI was calculated by normalizing FM (kg) by height squared (m^2). Patients were classified as obese if they met the NHANES 2009 criteria for class I obesity (male—FMI greater than 9 kg/m^2, female—FMI greater than 13 kg/m^2).[17] Table 1 shows a comparison of FMI and BMI based criteria for obesity. Agreement of obesity classification was assessed using the kappa statistic for obesity as categorized by BMI vs FMI.

Patients were then grouped according to combined SMI and FMI classifications of low SMI and high FMI (sarcopenic obese), normal SMI and high FMI (obese), normal SMI and FMI (normal), and low SMI and normal FMI (sarcopenic). Representative axial CT for patients in each group is shown in figure 1.

Statistical Analysis

We compared clinicopathological variables across the 4 groups. Continuous features were summarized with means (SD) or medians (IQR) as appropriate and compared using the t-test or Wilcoxon rank sum test. Categorical features were summarized with frequency counts (percentages), and compared using the chi-square and Cochran-Armitage trend tests.

Table 1. *Obesity classification criteria according to WHO classification of obesity by BMI and FMI generated from the NHANES cohort*

Category	BMI (kg/m^2)	Category	Male FMI (kg/m^2)	Female FMI (kg/m^2)
Underweight	Less than 18.5	Severe fat deficit, moderate fat deficit, mild fat deficit, normal	Less than 2, 2—less than 2.3, 2.3—less than 3, 3—6	Less than 3.5, 3.5—less than 4, 4—less than 5, 5—9
Normal	18.5—24.9			
Overweight (pre-obese)	25—29.9	Excess fat	Greater than 6—9	Greater than 9—13
Obese:	30.0 or Greater	Obese:	Greater than 9	Greater than 13
Class I (mild obesity)	30.0—34.9	Class I	Greater than 9—12	Greater than 13—17
Class II (moderate obesity)	35 — 39.9	Class II	Greater than 12—15	Greater than 17—21
Class III (morbid obesity)	40.0 or Greater	Class III	Greater than 15	Greater than 21