MALNUTRITION AND ITS RELATIONSHIP WITH SKELETAL MUSCLE INDEX IN PATIENTS WITH BLADDER CANCER UNDERGOING RADICAL CYSTECTOMY

By

Makena A. Whitaker

A THESIS

Presented to the Faculty of Graduate Programs in Human Nutrition
And the Oregon Health & Science University
School of Medicine
In partial fulfillment of
The requirements for the degree of

Master of Science in Clinical Nutrition

June 2017

School of Medicine

Oregon Health & Science University

CERTIFICATE OF APPROVAL

This is to certify that the Master's thesis of

Makena A. Whitaker

has been approved

Mentor: Julie McGuire, MS, RDN, LD

Member: Mark Garzotto, MD

Member: Jen-Jane Liu, MD

TABLE OF CONTENTS

List of Tables

List of Figures

Acknowledgment

First, I would like to thank my teacher, thesis mentor and program advisor, Julie McGuire, MS, RDN, LD of the Graduate Programs in Human Nutrition at Oregon Health & Science University (OHSU). The door to Mrs. McGuire's office was always open whenever I ran into troubled waters or had a question about my research or writing.

Second, I am grateful for my committee members, teachers, and urology research pioneers, Dr. Jen-Jane Liu of the Urology Surgery Service at OHSU and Dr. Mark Garzotto of the Urology Surgery Service at the VA Portland Health Care System, and OHSU School of Medicine for their research curiosity and support.

I would also like to thank the experts who were involved in the malnutrition assessment, Amanda Bryant, RD, LD of the Adult Cancer Nutrition Services at OHSU and skeletal muscle analysis and indexing, Jasper Bash, BS of the Medical School at OHSU. Additionally, I would like to thank Michael Lasarev, MS of the Oregon Institute of Occupational Health at OHSU as a statistics expert and second reader of this thesis. I am gratefully indebted to him for his insightful and valuable comments on my thesis.

Finally, I must express my profound gratitude to my parents and to my boyfriend, Lane Mehringer, for providing unfailing support and continuous encouragement through my years of study.

This accomplishment would not have been possible without them. Thank you.

Abstract

Background: Declines in nutrition status and changes in adverse body composition frequently occur in oncology patients including those with muscle invasive bladder cancer undergoing radical cystectomy (RC). Furthermore, RC frequently results in secondary surgical complications with as many as 60% of patients experiencing a complication within 90 days of surgery. Patient skeletal muscle and nutrition status assessed preoperatively may be predictors for adverse outcomes. The objective of this retrospective closed cohort study was to differentiate perioperative skeletal muscle area in patients with various nutrition statuses and describe hospital length of stay (LOS), readmission rates, and adverse surgical events after RC. *Methods:* Using diagnostic CT images, skeletal muscle index (SMI) at L3 was quantified and utilized as a marker for change in skeletal muscle and its association with mild to severe malnutrition in 43 patients with bladder cancer preoperatively. The Patient Generated Subjective Global Assessment (PG-SGA) was utilized to classify presence and severity of malnutrition. Patient adverse surgical events were classified using the Memorial Sloan-Kettering Secondary Surgical Events classification. *Results:* Half of all patients were at least 69 years old (48-87), majority were overweight (BMI >24.9), and 46% of patients were classified as moderately to severely malnourished. No significant trends were noted in SMI among mild or moderate-severe malnourished patients. Male SMI scores significantly decreased from baseline CT to recovery CT scan, while the same was not observed in female patients. No significant trends in rate of LOS, adverse surgical event grade, or readmissions among nutrition groups were observed. *Conclusions:* Loss of skeletal muscle mass and malnutrition is highly prevalent among patients with bladder cancer undergoing RC, however, further research is required to more adequately characterize multifactorial muscle loss during surgery treatment course and its association with standardized nutrition assessment tools.

Introduction

Radical cystectomy (RC), the gold standard surgical treatment for advanced bladder carcinoma, is a complex urological procedure with a postoperative complication rate as high as 60%. Multiple factors are associated with postoperative recovery including patient comorbidities, tumor burden, and surgical technique. For researchers and clinicians, it is a continuous challenge to determine patient suitability for RC.[1] Sarcopenia, the age associated loss of skeletal muscle mass and function, is an insidious process precipitated by several factors including normal aging, physical inactivity, inflammation, and malnutrition. Cross-sectional muscle area of the abdominal muscles, an accepted surrogate for sarcopenia, has been used to attempt to predict postoperative complications as well as morbidity and mortality after major surgical procedures, including within genitourinary surgical cohorts.[2,3] Malnutrition, as defined by the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Academy of Nutrition and Dietetics (AND), is a major catabolic process associated with longer hospital length of stay (LOS) and postoperative complications.[4] Geriatric patients have an increased risk for malnutrition as well as individuals with bladder cancer.[5] The average age of patient diagnosis with bladder cancer is 73 years old[6] and it is estimated that 17-57% of geriatric patients receiving care in hospitals and nursing homes suffer from malnutrition.[7]

Further clinical research is needed to explore malnutrition's role as a predictor for postoperative recovery, including length of hospitalization, postoperative complications, and readmission in radical cystectomy patients. The association between malnutrition and sarcopenia using standardized and validated measures has not been fully described. To address this gap, this study will investigate whether sarcopenia, as measured by preoperative skeletal muscle index (SMI) of the core muscle group at the 3rd lumbar vertebra (L3), is correlated with nutrition status, as measured by the Patient-Generated Subjective Global Assessment (PG-SGA), a validated nutritional assessment tool in oncology patients, at postop in all eligible bladder cancer patients receiving radical cystectomy surgery at Oregon Health & Science University (OHSU).

Specific Aims and Hypotheses

Aim 1: To determine if the SMI of core muscles (rectus abdominus, abdominal, psoas, and paraspinal muscles) at L3 using computed tomography scan (CT) is correlated with nutrition status, as measured by the PG-SGA.

Hypothesis 1: Subjects diagnosed with a greater severity of malnutrition will have a significantly decreased skeletal muscle index compared to well-nourished patients.

Aim 2: To determine if the degree of malnutrition, as measured by the PG-SGA, is associated with the prevalence of postoperative complications, length of hospitalization, and 30- and 90-day readmissions among subjects undergoing radical cystectomy and urinary diversion.

Hypothesis 2: Postoperative complications, length of hospitalization, and 30-day and 90-day readmissions will be significantly greater among subjects with greater severity of malnutrition.

Aim 3: To characterize the change in degree of sarcopenia, evaluated by SMI perioperatively, and the difference in SMI change among subjects with malnutrition.

Hypothesis 3: SMI will decrease from baseline to post radical cystectomy for all patients, but the reduction will be more pronounced among those with more severe malnutrition.

Background

Bladder Cancer and Radical Cystectomy

Bladder cancer is ranked the 4th most prevalent type of cancer in men with the mean age of 73. Bladder cancer disproportionately occurs in men with 35.8 new cases annually per 100,000 persons compared to 8.7 new cases for females. 60% of all bladder malignancies in the U.S. occur in adults ≥ 65 years.[8] With the aging population in the United States (U.S) expanding, it can be expected that bladder cancer will continue to place a significant burden on the healthcare system. At the time of diagnosis, about 1 in 3 bladder cancers have invaded into deeper layers of the bladder wall requiring surgery.[6] Surgical intervention is a standard treatment for muscle invasive bladder cancer to increase survival and may also be used as a palliative treatment strategy. The 'gold standard' surgical procedure performed for muscle invasive bladder cancer is radical cystectomy (RC), a complex urologic procedure involving the removal of the bladder and other organs, including the prostate in men. On average, the length of hospitalization for RC patients in the U.S. is 10 days.[9] Surgical morbidity and complication rates following RC and urinary diversion are significant with complication rates of 40-60% and mortality rates as high as 8-11% in the first 90 days after surgery.[10-12] An estimated 15-20% of RC patients experience a major complication requiring reoperation or intensive care unit (ICU) admission.[13] Surgical outcomes are affected by many factors including patient comorbidities, tumor burden, and surgical technique. It can be difficult to determine patient readiness for RC surgery and to predict which patients will suffer from postoperative complications and morbidity. Therefore, it is essential to consider tools to better predict which patients are at higher risk for poor surgical outcomes. Core muscle measurements are surrogate markers for sarcopenia, which have been increasingly researched as predictors of impaired hospital LOS, postoperative complication, and impaired survival. Nutrition status may also be an important predictor and modifiable risk factor for postoperative complications in hospitalized and surgical patient cohorts.

Sarcopenia

Definition

The International Sarcopenia Consensus Conference Working Group defines sarcopenia as the age-associated loss of skeletal muscle mass and function alone, or in combination with an increase in fat mass. Sarcopenia is precipitated by aging, genetics, a decrease in physical activity, change in endocrine function including insulin resistance, chronic disease (secondary sarcopenia), inflammation, and malnutrition.[14] In the absence of a disease state or injury, sarcopenia results in a 3-8% reduction in muscle mass per decade after the age of 30.[15,16] The loss of muscle mass is more pronounced in men than in women. Although women may be protected in earlier years, they can experience a steeper decline in later adulthood and old age.[17] Sarcopenia is an insidious process, which over time can be debilitating and is associated with increased risk of falls and inability to perform activities of daily living.[14,18] Acute or chronic illness, injury, physical inactivity, and malnutrition or inadequate intake of protein can hasten lean body mass catabolism and further risk of functional impairment.[19,20]

Other conditions commonly experienced by elderly populations, such as cachexia and frailty, have similar definitions as sarcopenia and include many of the same physical manifestations of frailty and cachexia such as weight loss, decreased physical activity, low gait speed, exhaustion, and weakness. However, frailty also encompasses psychosocial aspects such as cognitive status.[21] Cachexia and age-related sarcopenia are associated with similar changes in body composition such as the loss of lean body mass and fat mass. However, cachexia is defined by increased protein catabolism due to disease(s), chronic or recurrent systemic inflammation, and in some cases, decreased nutrient availability related to reduced food intake and/or impaired absorption and nutrient losses.[5]

Diagnosis & Prevalence

Diagnostic criteria for sarcopenia has not been fully described. Endorsed by the ESPEN, recommendations by the European Working Group on Sarcopenia in Older Persons,[22] as well as the statement from the ESPEN Special Interests Groups of Cachexia in Chronic Disease and Nutrition in Geriatrics[5] indicate that the diagnosis of sarcopenia should be based on the combination of decreased muscle mass and strength and/or function (i.e. low gait speed).

Muscle mass can be estimated by any validated technique such as dual energy X-ray absorptiometry (DEXA), bio-electric impedance analysis (BIA) or computed tomography (CT) scanning. Baumgartner et al. in the New Mexico Study, quantified sarcopenia by indexing appendicular skeletal fat-free mass (FFM) relative to stature[18]. It was measured by DEXA in healthy Hispanic and non-Hispanic whites. Decreased muscle mass in kg/m^2 was defined as ≥2 standard deviations below the mean measured in healthy adults $<$ 30 years old of the same sex and ethnic background.[18] Combining data from the New Mexico study previously mentioned and a similar study, Morley et al. analyzed sarcopenia prevalence in a mixed cohort of 630 lean and obese individuals aged 60+ years. The prevalence of sarcopenia, in women aged 60-70 years was 7% compared to 12% in 80+ women. In men, the prevalence of sarcopenia was 14% in those aged 60-70 years old compared to 23% among those 80+ (n=630).[23] Janssen et al. using BIA data to index FFM/fat mass (FM) (-2 SD) from the National Health and Nutrition

Examination Survey (NHANES) III found the prevalence of sarcopenia was 7-10% for both women and men ≥60 years of age (n=4504).[24]

Abdominal CT preferred in surgical oncology settings as it is part of routine evaluation.[25,26] Surgeons can measure cross-sectional area of core muscle to utilize as a predictor for surgical outcomes. By measuring cross-sectional area of core muscles on preoperative CT, researchers established cutoffs for the presence or absence of sarcopenia in men and women. Prado et al. defined presence of sarcopenia with assessment of L3 skeletal muscle index ≤38.55 cm^2/m^2 for women and ≤53.4 cm^2/m^2 for men.[25] The L3 region contains the psoas, paraspinal muscles, and abdominal wall muscles. Subjects that fell below these cut-offs were at greater risk for death, diminished functional status, and chemotherapy toxicity in a population of sarcopenic obese patients with cancers of the respiratory and gastrointestinal (GI) tract (n=250).

Skeletal Muscle Mass and Surgical Outcomes

Hasselager et al. examined eight published trials evaluating the effect of core muscle size on postoperative outcomes in patients undergoing major abdominal surgery. Six of these studies specifically measured total psoas area (TPA) and the remaining two measured total abdominal muscle area, both surrogates for sarcopenia. Three (3) of the studies observed a significant increased risk in complications for patient groups with greater sarcopenia. To define sarcopenia, two out of these same three studies compared quartiles of TPA and one study used a cut–off of ≤ 50 cm^2/m^2. Additionally, lower TPA was linked to longer length of hospitalization (67%, n=3 studies), and an increase in long-term mortality (86%, n=7). Six out of the eight studies published by Hasselager et al. showed a significantly increased long-term mortality and two out of these studies found a significantly longer LOS related to core muscle size. [27]

Smith et al. evaluated the effect of TPA on immediate and 30-day postoperative complications in a cohort of 200 patients treated with radical cystectomy. To determine the presence or absence of sarcopenia, Smith et al. established TPA cutoff points for both men and women (52.3 cm^2/m^2, AUC=0.70 and 65.3 cm^2/m^2, AUC=0.51, respectively). Using this criterion, although stratification was not clinically significant, subjects in the sarcopenic group were more likely to experience a higher 30-day complication rate (30 vs. 16%; p=0.03). This difference was even greater in the cohort of women (43 vs. 11*%;* p=0.008). Sarcopenic patients had more than twice the odds of experiencing 30-day major complications when compared to non-sarcopenic counterparts (OR 2.25; 95% CI: 1.11—4.56; p=0.02). Sarcopenic females showed a trend, albeit not significant, towards increased length of hospitalization. Overall, there was no association between complication rate and TPA as a continuous variable and hospital readmission rates were similar between sarcopenic/non-sarcopenic groups.[2] Similarly, Ahmadi et al. evaluated associations between TPA and 30-day and 90-day major complication rates in a cohort of 466 bladder cancer patients treated with RC. Ahmadi et al. observed that each additional 1 cm^2/m^2 increase in TPA was associated with a 6% decrease in the 90-day complication rate.[1]

For researchers and clinicians, it is a continuous challenge to identify which patients will make successful surgical candidates, especially in the elderly cohort. Modifiable risk factors such as physical activity, smoking, and diet may modulate surgical outcomes and provide opportunities for patient pre-habilitation. Malnutrition is a major catabolic stressor, which, if accurately assessed using standard procedures, may allow clinicians to make properly informed decisions on patient candidacy for high-risk surgeries. Within the nutrition care process, the assessment of malnutrition that closely involves the patient may promote healthier eating and physical activity to improve perioperative outcomes.

Malnutrition

Definition, Diagnosis, and Prevalence

Malnutrition in adult hospitalized cancer patients is a common condition, with as many as 50-80% of patients diagnosed with cancer classified at risk of moderate or severe malnutrition.[7] Malnutrition in adult *outpatient* oncology patients is more difficult to estimate as nutrition screening in these patients is not standardized across institutions and performed less frequently, however, it has been estimated as high as 32%.[28] Both the ASPEN and the AND define disease-related malnutrition as "an acute, subacute or chronic state of nutrition, in which a combination of varying degrees of overnutrition or undernutrition with or without inflammatory activity has led to a change in body composition and diminished function".[29] In order to diagnose moderate or severe adult malnutrition, AND/ ASPEN recommend the identification of at least two of the following six characteristics: inadequate energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat, local or generalized fluid accumulation, and/or diminished functional status determined by handgrip strength. AND/ ASPEN also advise that clinicians should expect to see changes in malnutrition screening and diagnosis as evidence is systematically collected, analyzed, and disseminated.[4] Malnutrition is recognized as a major preoperative risk factor and an important predictor of postoperative outcomes for surgical patients. Gillis et al. found 30-day readmission rates were greater in malnourished outpatients (n=70) undergoing elective colorectal surgery (23% vs. 7%).[30] Similarly, Hand et al. found that after adjusting for disease severity and use of healthcare services malnourished adult inpatients (n=39) had a 75% longer length of hospitalization.[31] The association between malnutrition and poor surgical outcomes including increased length of hospitalization and mortality rate is well established in GI surgeries.[32,33] However, there are few studies examining malnutrition and urological surgical outcomes. Furthermore, institutions use varied diagnostics to identify and document malnutrition in both clinical and research settings making reliable comparisons across cohorts challenging. The clinical screening tool, the PG-SGA, developed specifically for cancer patients is recognized by AND/ ASPEN and is the malnutrition assessment tool in our patient population.[34]

PG-SGA as an Oncology Nutrition Assessment Tool

There are several nutrition assessment tools acknowledged by AND/ ASPEN including the Mini Nutritional Assessment (MNA), Subjective Global Assessment (SGA), and the PG-SGA. The PG-SGA was adapted in the mid-1990s from the SGA, which was originally developed for patients undergoing GI surgery. The PG-SGA is unique from the SGA as it includes symptomatology assessment more specific to the cancer population and is designed for partial completion by the patient. The patient section was added to streamline data collection for the examiner and to involve and empower the patient.[34] The first four sections of the PG-SGA are comprised of patient history (weight loss, dietary intake, GI symptoms and functional capacity), which can be completed by the patient. The last three sections are completed by the health professional, which include metabolic demand, disease diagnosis, and a nutrition-related physical exam

(NFPE) to examine fat, muscle stores and fluid status. Each section of the PG-SGA is awarded 0-4 points based on the impact of each symptom. The scored PG-SGA yields both a quantitative score (0-50 with ≥ 9 points indicates need for critical nutrition intervention) and qualitative categorizations (A = well-nourished, B = mild to moderately malnourished, and C= severely malnourished). By administrating the PG-SGA, clinicians are able to standardize nutrition assessment and may better inform surgical team on perioperative outcomes.

PG-SGA/SGA Predict Length of Hospital Stay, Readmission, and Prognostic Outcomes

In an observational study of 682 inpatients, Guerra et al. observed an increased length of hospitalization in patients diagnosed with moderate (PG-SGA grade B) (HR 0.60, 95% CI: 0.49—0.73) and severe malnutrition (PG-SGA grade C) (HR 0.52, 95% CI: 0.42—0.64).[35] Although the PG-SGA has recently been recognized as an important predictor in oncology patients, the parent assessment tool, the SGA, has consistently been observed as a predictor for length of hospital stay (LOS), readmission and prognosis in other populations. Jeejeebhoy et al. observed a longer length of hospitalization (OR: 2.19; 95% CI: 1.28—3.75) and greater 30-day readmission rate (OR: 2.12; 95% CI: 1.24—3.93) in hospitalized medical and surgical patients (n=733) diagnosed with severe malnutrition (SGA grade C).[36] In a large observational study of acute hospitalized patients (n=3122) with a mean age of 65 $\pm$ 18 years, malnourished patients (diagnosed by SGA) had a greater 90-day length of hospitalization (15 vs. 10 days) and a greater 90-day readmission rate (36 vs. 30%). The SGA may also offer prognostic information for hospitalized patients. Lim et al. observed that mortality was higher in malnourished patients at one year (34% vs. 4.1 %), two years (42.6% vs. 6.7%) and three years (48.5% vs. 9.9%); p<0.001 for all. Overall, malnutrition was a significant predictor of mortality (adjusted HR=4.4, 95% CI:

3.3—6.0, p<0.001). Lim et al. also found malnourished patients had longer hospital stays (6.9±7.3 days vs. 4.6±5.6 days) and were more likely to be readmitted within 15 days.[37]

A growing body of literature shows TPA and SMI are strong predictors of postoperative outcomes. The purpose of this study was to examine the relationship between sarcopenia and malnutrition measured preoperatively using standardized and validated assessment tools. If the PG-SGA can identify patients with decreased skeletal muscle index or vice versa, they may be used as proxy for one another to determine baseline nutrition and muscle store status. Additionally, our study was designed to compare length of hospitalization, 30- and 90-day readmission, and postoperative complication rates among well-nourished/mild malnutrition (PG-SGA stage A) and moderate to severe malnutrition (PG-SGA stage B and C) groups.

Methods

General Design

We performed a retrospective closed cohort study by identifying patients who underwent RC and urinary diversion for treatment of bladder cancer and were simultaneously followed by the outpatient Registered Dietitian Nutritionist (RDN) through the OHSU Urology Clinic. Study subjects originated from a database of all patients that the RDN had assessed in clinic between 2014 and 2016. All subject data was obtained from the electronic medical record (EMR) and the institutional cystectomy database.

All protocols had been previously approved by the Oregon Health & Science University Institutional Review Board (IRB) for an earlier study titled *Predictive Factors and Outcomes of Patients Diagnosed and Treated for Bladder Cancer (IRB00010437)*. This retrospective study was granted exemption from obtaining participant consent given that the study variables were collected as part of routine clinical care.

Setting and Study Population

The study population included all eligible patients who underwent RC for bladder cancer at OHSU and attended a comprehensive outpatient oncology nutrition clinic visit prior to surgery. Since 2014, all new patients scheduled to receive RC treatment consult with the RDN to complete a 30-45-minute in-patient or phone preoperative nutrition assessment. During this assessment, the PG-SGA is completed to identify current malnutrition risk and degree of malnutrition, if present.

Enrollment

Subjects deemed eligible for the study met the following inclusion and exclusion criteria:

<table>
<tr><th>Inclusion Criteria</th><th>Exclusion Criteria</th></tr>
<tr><td>Diagnosed with bladder cancer requiring a radical cystectomy with urinary diversion</td><td>Not screened by PG-SGA</td></tr>
<tr><td>2 CT scans taken pre/post-surgery</td><td rowspan="4">No CT imaging available at L-3 or CT imaging unsuitable for measurement purposes</td></tr>
<tr><td>Attended or called in for ≥1 preoperative outpatient clinic appointment with Registered Dietitian</td></tr>
<tr><td>Completed Patient-Generated Subjective Global Assessment (PG-SGA) prior to surgery</td></tr>
<tr><td>Between 18 and 95 years of age</td></tr>
</table>

Confidentiality

All information abstracted from the institutional database or the EMR system remains strictly confidential. Study investigators were the only personnel with access to data. All data associated with patient identifiers is stored on secure, password-protected, OHSU network computers, OHSU approved cloud storage via Box, or in a securely locked file cabinet. Any data stored in other locations is de-identified using randomly generated number identifiers.

Determining Skeletal Muscle Index

Skeletal muscle area (SMA) was measured on an axial CT section obtained during abdominal CT or PET/CT imaging as part of the standard of care. The preoperative SMA was measured on the preoperative CT image nearest to time of surgery and postoperative SMA was measured on follow-up images $\geq$ 90 days after surgical date if available or nearest to that time period. Using these scans, a single trained examiner measured SMA or the cross sectional area of the L3 muscle group including the external oblique, internal oblique, transversus abdominis, rectus abdominus, psoas,quadratus lumborum, and erector spinae. The borders of muscles of interest were identified by OsiriX® analysis software (version 5.8 PIxemo SARL, Geneva, Switzerland) to generate SMA based on predefined Hounsfield units between -29 to 150. Further, SMA measures were normalized by the patient's height (m^2) to determine SMI in cm^2/m^2 perioperatively and a relative SMI score. Relative SMI was calculated for each sex as follows: relative SMI= (SMI)/ (sex-specific median SMI). The change in SMI was calculated as follows: change in SMI = (postoperative SMA – preoperative SMA).

Nutrition Assessment

The PG-SGA was used to identify malnutrition risk and degree of malnutrition. PG-SGA was categorized into two classifications: well-nourished or mild (Stage A) or moderate/severe (Stage B/C). Moderate and severe categories were combined due to the small sample size.

Surgical Complication or Adverse Event Grades

All postoperative adverse events were captured for each subject. The Memorial Sloan Kettering (MSK) Cancer Canter Complication grading system[11] was used to assess the severity of any adverse event postoperatively (intraoperative events were excluded). The grading system is as follows: Grade 0: No event; Grade 1: Use of oral medications or bedside intervention; Grade 2: Use of intravenous medications, TPN (Total Parenteral Nutrition), EN (Enteral Nutrition), or blood transfusions; Grade 3: Interventional radiology, therapeutic endoscopy, intubation, angiography; Grade 4: Residual and lasting disability requiring major rehabilitation or organ resection, Grade 5: Death as result of complication(s).

Statistical Analysis

Data was collected using Microsoft Excel and stored via a secure OHSU Box account as previously described. Data analyses included descriptive statistics of all subjects including sex, race, height, weight, BMI, age-adjusted Charlson Comorbidity Index (CCI; adjusted by 1 additional point for each decade >50 years), clinical tumor stage (T stage), type of bladder cancer, type of urinary diversion, and type of surgery. Means, medians, standard deviations, and ranges were calculated for continuous outcome variables including SMI of L3 muscle groups and 90-day readmission rates. Categorical outcome variables included PG-SGA classification groups (mild or moderate/severe), 30-day and 90-day MSK complication grades. All data was computed using STATA statistical software. Statistical tests included t-tests, Mann-Whitney, and Peto-Peto tests for significance as appropriate as well as linear regression techniques to determine interactions between continuous and discrete variables. *P*-values <0.05 were considered significant.

Results

Demographics

Forty-eight (48) subjects underwent RC for bladder cancer between 2014 and 2016 and were considered eligible for this analysis. There were 26 subjects defined as well-nourished/mild malnutrition (Stage A) and 22 defined as moderately or severely malnourished (Stage B or C) by the PG-SGA. The moderate and severe categories were combined due to the small sample size of subjects. The majority of subjects were white (89.6%), male (64.6%), and had a BMI ≥25 (70.8%) (Table 1). Subjects' age ranged from 48-87 years; half the sample was at least 68.5 years. Co-morbidities were described using age-adjusted CCI. The majority of subjects had an age-adjusted CCI ≥ 3-6 (70.8%) which describes subjects with several comorbidities.

Table 1. Selected Demographic Characteristics

		PG-SGA Malnutrition Grade	
		Mild	Moderate or Severe
	Total	(Stage A)	(Stage B or C)
Characteristic	(n=48)	(n=26)	(n=22)
Age (yrs),[a] median (range)	68.5 (48-87)	65 (48-87)	72.5 (54-83)
Age category (yrs)			
< 55	3 (6.3)	2 (7.7)	1 (4.5)
≥ 55-64	15 (31.3)	11 (42.3)	4 (18.2)
≥ 65-74	18 (37.5)	8 (30.8)	10 (45.5)
≥ 75-84	11 (22.9)	4 (15.4)	7 (31.8)
≥ 85	1 (2.1)	1 (3.8)	0
Race/Ethnicity			
White	43 (89.6)	23 (88.5)	20 (91.0)
Other[b]	5 (10.4)	3 (11.5)	2 (9.0)
Sex			
Male	31 (64.6)	19 (73.1)	12 (54.5)
Female	17 (35.4)	7 (26.9)	10 (45.5)
BMI, kg/m^2			
Normal (18.5-24.9)	14 (29.2)	7 (26.9)	7 (31.8)
Overweight (25-29.9)	17 (35.4)	8 (30.8)	9 (40.9)
Obese (30+)	17 (35.4)	11 (42.3)	6 (27.3)
Age-Adjusted CCI[c]			
< 3	0	0	0
≥ 3-6	34 (70.8)	22 (84.6)	12 (54.5)
≥ 7	14 (29.2)	4 (15.3)	10 (45.5)

A comparison of baseline characteristics between subjects who underwent radical cystectomy with mild (n=26) to moderate/severe malnutrition (n=22). Values expressed as n (%) unless noted otherwise.

[a] At time of surgery.

[b] Includes Black, Hispanic, Asian, or Undeclared.

[c] Adjusted by 1 additional point for each decade >50 years.

Abbreviations: PG-SGA, Patient Generated Subjective Global Assessment; CCI, Charlson Comorbidity Index; BMI, body mass index.

Pathological & Surgical Characteristics

Forty-eight (48) subjects underwent RC for urothelial bladder carcinoma and one subject underwent RC for pure squamous bladder carcinoma (Table 2). Twenty-six subjects (56%) received neoadjuvant chemotherapy and 35 subjects (72%) underwent RC with a clinical tumor stage of T2. Forty-one (41) subjects underwent RC with conduit urinary diversion and seven with continent urinary diversion.

Table 2. Pathological & Surgical Characteristics

		PG-SGA Malnutrition Grade	
Characteristic	Total (n=48)	Mild (Stage A) (n=26)	Moderate or Severe (Stage B or C) (n=22)
Neoadjuvant Chemotherapy			
None	26 (54.2)	12 (46.2)	14 (63.6)
Any	22 (45.8)	14 (53.8)	8 (36.4)
Clinical Tumor Stage			
T1 or Tis	12 (25.0)	7 (26.9)	5 (22.7)
T2	35 (72.9)	19 (73.1)	16 (72.7)
T3	1 (2.1)	0	1 (4.5)
Bladder Carcinoma			
Urothelial	47 (97.9)	25 (96.2)	22 (100)
Pure Squamous	1 (2.1)	1 (3.8)	0
Robotic Assistance			
Yes	18 (37.5)	13 (50)	5 (22.7)
No	30 (62.5)	13 (50)	17 (77.3)
Urinary Diversion			
Conduit	41 (85.4)	21 (80.8)	20 (90.9)
Continent	7 (14.6)	5 (19.2)	2 (9.1)

A comparison of pathological and surgical characteristics between subjects who underwent radical cystectomy with mild (n=26) to moderate/severe malnutrition (n=22). Values expressed as n (%). Abbreviations: PG-SGA, Patient Generated Subjective Global Assessment

Preoperative & Postoperative Skeletal Muscle Index

SMI was measured in male and female subjects prior to RC on pelvic/abdominal CT (n=43) and post-RC (n=33) (Table 3). Five subjects did not have utilizable preoperative (pre-op) CT scans, 15 subjects did not have utilizable postoperative (post-op) scans, and four subjects were missing both. Mean SMI and mean relative SMI score was calculated by sex and separately among both malnutrition groups. Relative SMI score was used to compare the subject's score in relation to the median SMI measure in both males and female cohorts.

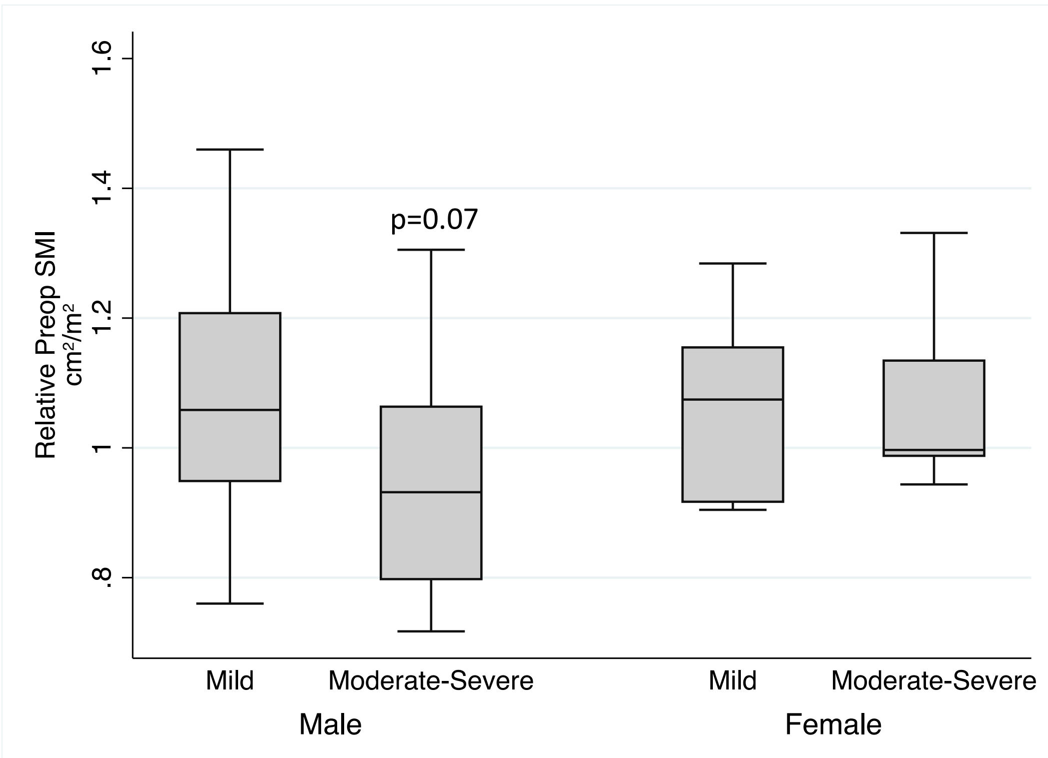
Table 3. Skeletal Muscle Index

	PG-SGA Malnutrition Stage		
Characteristic	Mild Stage A	Moderate or Severe Stage B or C	P
Pre-op SMI, cm^2/m^2			
Male (n=29)	52.0 $\pm$ 9.6 (36.4-70.0)	45.3 $\pm$ 8.0 (34.4-62.6)	
Female (n=14)	44.6 $\pm$ 6.7 (37.8-53.7)	43.4 $\pm$ 7.0 (31.4-55.7)	
Pre-op Relative SMI Score[b]			
Male (n=29)	1.1 $\pm$ 0.2 (0.8-1.5)	0.9 $\pm$ 0.2 (0.7-1.3)	0.07[a]
Female (n=14)	1.1 $\pm$ 0.2 (0.9-1.3)	1.0 $\pm$ 0.2 (0.7-1.3)	0.9[a]
Post-op SMI, cm^2/m^2			
Male (n=25)	50.7 $\pm$ 12.2 (34.5-76.7)	44.1$\pm$ 8.6 (33.5-55.7)	
Female (n=8)	50.1 $\pm$ 10.2 (42.9-57.3)	44.4 $\pm$ 7.6 (35.8-52.9)	
Post-op Relative SMI Score[b]			
Male (n=25)	1.1 $\pm$ 0.3 (0.8-1.7)	1.0 $\pm$ 0.2 (0.7-1.2)	0.2[a]
Female (n=8)	1.1 $\pm$ 0.2 (1.0-1.3)	1.0 $\pm$ 0.2 (0.8-1.2)	0.5[a]

A comparison of pre/post SMI measures between subjects who underwent radical cystectomy with mild to moderate/severe malnutrition. Values expressed as mean $\pm$ SD (range).
[a] Mann-Whitney, [b] Relative SMI Score was calculated by measuring skeletal muscle area of core muscle area at L3 and normalizing by patient height and sex-specific median SMI.
Abbreviations: SMI, Skeletal Muscle Index, PG-SGA, Patient Generated Subjective Global Assessment

The distribution of pre-op and post-op relative SMI (SMI/median SMI) did not significantly differ among men (Mann-Whitney; p=0.07) or women (p=0.9) preoperatively, or among males (p=0.2) and females postoperatively (p=0.5) for each malnutrition group (Table 3). Albeit not significant, subjects in the moderate/severe malnutrition group tended to have a decreased pre-op SMI compared to the mild group; this trend was more pronounced in men compared to women (n=43). A man with mild malnutrition had a 70% (95%CI: 50-90%) chance of having a greater relative pre-op SMI compared to a man with moderate/severe malnutrition. Distribution of relative pre-op SMI score was illustrated using box-whisker plots by sex for each malnutrition group (Figure 1).

Figure 1. Malnutrition and Relative Preoperative Skeletal Muscle Index



F1. Distribution of Relative Preoperative Skeletal Muscle Index (SMI) by sex of subjects with mild to moderate/severe malnutrition (n=43; 29 males, 14 females). SMI was calculated by measuring skeletal muscle area of core muscle area at L3 using CT and normalizing by patient height to find skeletal muscle index (SMI). Relative SMI is standardized by the sex-specific median SMI. Malnutrition grade was captured by the Patient Generated Subjective Global Assessment (PG-SGA) prior to RC. Mann-Whitney test between malnutrition groups for each sex *p>0.05.* An α level of < 0.05 was considered significant for all statistical tests.

Perioperative Change in Skeletal Muscle Index

For our third aim, we calculated the mean change in pre-op SMI and post-op SMI (change in SMI = (post-op SMI) – (pre-op SMI)) for each subject among sex and malnutrition subgroups (Table 4). Due to missing or unusable scans, only 32 subjects were included in this analysis. Twenty-two subjects (69%) showed a decrease from baseline or pre-op SMI to post-op SMI, whereas 10 subjects (32%) showed an increase from baseline SMI to post-op SMI. The time between pre-op CT scan to RC surgery and time from RC surgery to post-op CT scan varied considerably between subjects. The median time from pre-op CT scan to RC was 39 days and ranged between 2-105 days. The median from time RC to post-op CT scan was 117.5 days and ranged between 15-648 days. Five subjects (15%) had post-op CT scans less than 90 days from surgery date. Given the wide range of days between RC and CT, the analysis was completed with non-parametric tests as appropriate.

Table 4. Mean Change in SMI during the Surgical Treatment Period

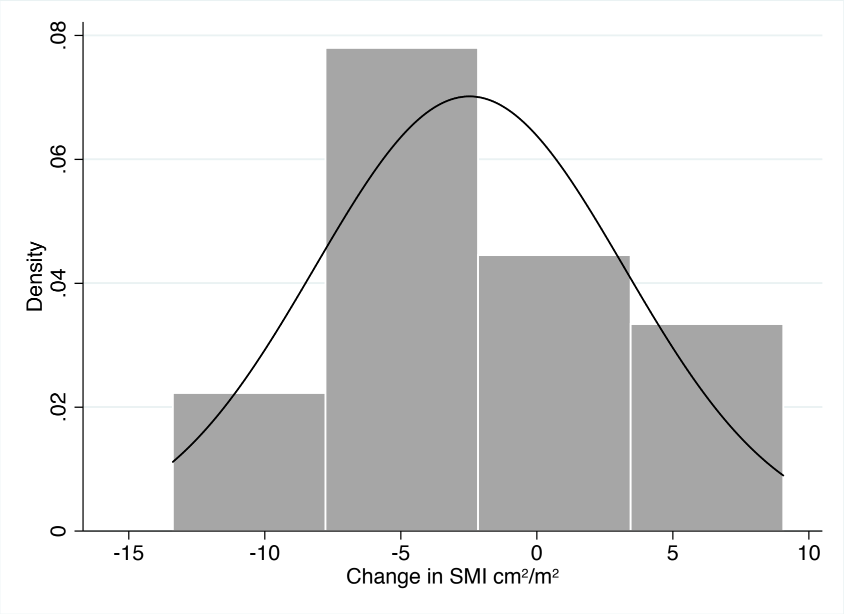
By Sex		
Males (n=24)	Females (n=8)	P
-2.6 ± 4.9 (-13.4 to +9.1)	-0.4 ± 4.4 (-6.2 to +5.1)	0.3[a]

By PG-SGA		
Mild Stage A (n=16)	Moderate or Severe Stage B or C (n=16)	P
-2.5 ± 5.7 (-13.4 to +9.1)	-1.6 ± 3.9 (-8.1 to +5.1)	0.6[a]

Comparison of subject's mean change in SMI during the surgical treatment period for subjects (n=32) by sex and PG-SGA malnutrition grade. Data displayed as mean ± SD (range).
[a]Two-sample t test with equal variance between mean change in SMI for sex or malnutrition stage
Change in SMI was calculated as follows: change in SMI = (postoperative SMI) – (preoperative SMI for each subject). Malnutrition grade was captured by the preoperative Patient Generated Subjective Global Assessment.
Abbreviations: SMI, Skeletal Muscle Index, PG-SGA, Patient Generated Subjective Global Assessment

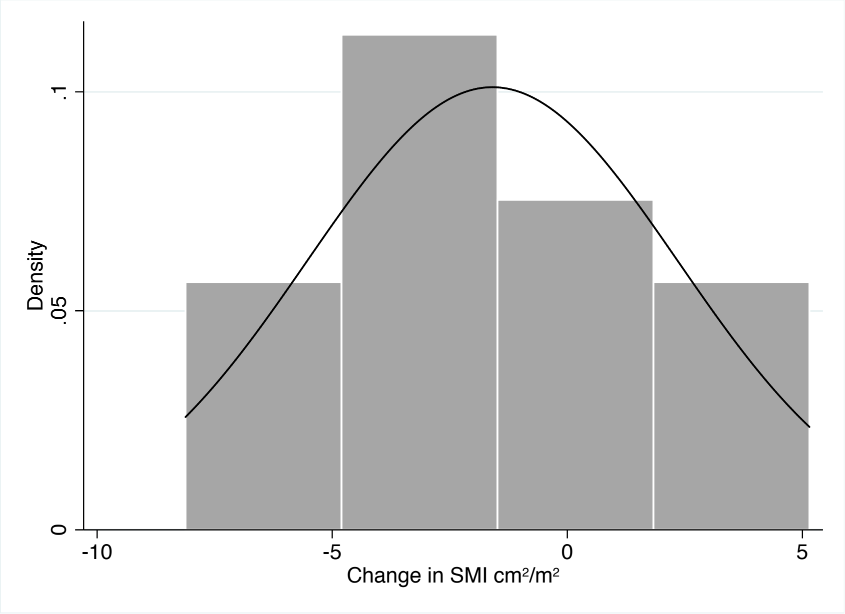
We compared the mean change in SMI from baseline among males (n=24) and females (n=8) and among mild (n=16) and moderate-severe (n=16) malnutrition groups. Using a two-sample t-test with equal variance, mean change in SMI was not significantly different between sexes or malnutrition groups (Table 4). The mean change in SMI in males (-2.6 ± 4.9 (-13.4 to +9.1)) was more severe compared to females (-0.4 ± 4.4 (-6.2 to +5.1)). However, the male group had a wider range of change in SMI and larger cohort size. The mean change in SMI was more severe in the mild group than the moderate-severe group. The distribution of mean change in SMI for each malnutrition group is given in Figures 2, 3.

Figure 2. Change in SMI in Subjects with Mild Malnutrition



F2. Distribution of change in SMI (cm^2/m^2) from baseline among subjects with mild malnutrition. Change in SMI was calculated as follows: change in SMI= (postoperative SMI) – (preoperative SMI for each subject). Malnutrition grade was captured by the preoperative Patient Generated Subjective Global Assessment (PG-SGA).

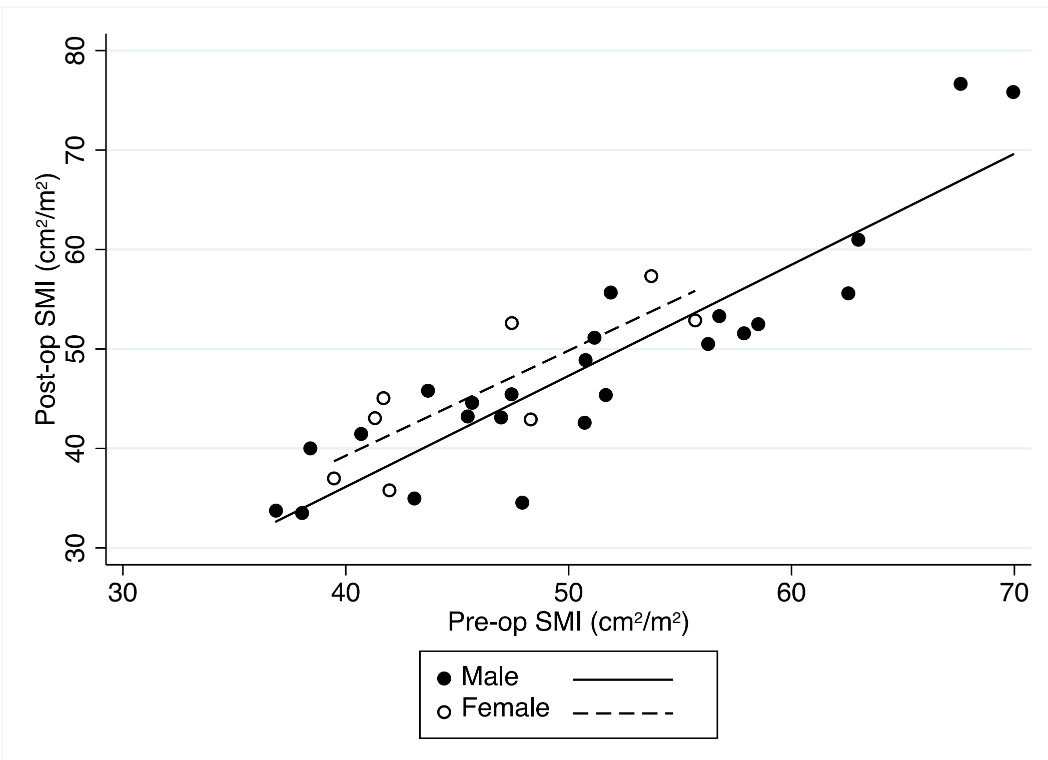
Figure 3. Change in SMI in Subjects with Moderate-Severe Malnutrition



F3. Distribution of change in SMI (cm^2/m^2) from baseline among subjects with moderate-severe malnutrition. Change in SMI was calculated as follows: change in SMI = (postoperative SMI) – (preoperative SMI for each subject). Malnutrition grade was captured by the preoperative Patient Generated Subjective Global Assessment (PG-SGA).

There was a strong linear association in post-op and pre-op SMI in both male (n=24) (*r*=0.9) and female (n=8) (*r*=0.8) groups. For every 1-unit increase in pre-op skeletal muscle index, there was an estimated 1.11 increase in post-op SMI for males and an estimated 1.06 increase for females (Figure 4). Based on results from a paired t-test, mean pre- vs post-SMIs were significantly different among individual subjects (n=32) (t=-2.38, p=0.02). However, we are unclear as to the clinical significance of this change.

Figure 4. Perioperative Skeletal Muscle Index



F4. Relationship between preoperative and postoperative skeletal muscle index (SMI) for male (n=25) and female (n=8) groups. SMI Score was calculated by measuring skeletal muscle area of core muscle area at L3 and normalizing by patient height. Pearson's correlation coefficient (r) for males = 0.9 and for females =0.8.

Clinical Characteristics

Hospital time to discharge (n=48), 30-day and 90-day incidence of readmission (n=47), 30-day and 90-day MSK complication grades (n=45), and pre-op consumption of immunonutrition supplement (n=46) were estimated for all subjects (Table 5). All patients had discharged from the hospital within the analysis time frame. The median subject time to discharge was five days (minimum of four days and maximum of 69 days). There were 12 total readmissions within the 90-d time period, eight of the 12 readmissions occurred within 30 days, and some subjects were readmitted more than once. A single patient was lost to follow up for 90-day analyses of incidence of readmission. The 30-day and 90-day complication grades were analyzed as frequency and proportions (Table 5) and complications were also analyzed by individual type of event (Table 6). For the 90-day complication grade analysis, three subjects were lost to follow-up.

Impact Advanced Recovery (AR)®, an immunonutrition supplement, is recommended pre-operatively to all eligible patients by the RDN (three servings daily for five days before RC). Additionally, Impact AR® is recommended in the post-op period but only pre-op consumption data was collected.

Table 5. Hospital Stay & Adverse Events

Characteristic	PG-SGA Malnutrition Stage: Mild Stage A(n=26)	Moderate or Severe Stage B or C (n=22)	P
Time to Discharge (days), median (range)	5 (4-69)	5 (4-21)	0.3[a]
Incidence of Readmission			0.06[a]
By post-op day 30	1 (4) (0.6—25.2)	7 (32) (16.6-—55.4)	
By post-op day 90	4 (16) (6.3—37.2)	8 (37) (20.1—59.7)	
30-day Complication Grade			0.2[b]
0-1	21 (43.8)	14 (29.2)	
2-3	5 (10.4)	7 (14.6)	
4-5	0	1 (2.1)	
90-day Complication Grade			0.6[b]
0-1	21 (46.7)	19 (42.2)	
2-3	1 (2.2)	3 (6.7)	
4-5	1 (2.2)	0	
Missing	3 (6.7)	0	
Consumed Immunonutrition Supplement[c]			
None	9 (18.8)	4 (8.3)	
Any	16 (33.3)	17 (35.4)	
Unknown	1 (2.1)	1 (2.1)	

A comparison of time to discharge, time until hospital readmission (≥ 1 24 hours) within 90-days from surgery, and post-op adverse events within 30 and 90 days from surgery using the MSKCC grading system, pre/post SMI measures between subjects who underwent radical cystectomy with mild (n=26 unless otherwise noted) to moderate/severe malnutrition (n=22 unless otherwise noted). Values expressed as n (%) (95% CI) unless noted otherwise.

[a] Peto-Peto, [b] Mann-Whitney, [c] Proportion of subjects who reported consuming recommended Impact Advanced Recovery Supplement® (3 servings daily for 5 days) prior to surgery. [d] Relative SMI Score was calculated by measuring skeletal muscle area of core muscle area at L3 and normalized by patient height and sex-specific median SMI. A single patient was lost to follow up for 90-day incidence of readmission (n=47). 3 subjects lost to follow-up for 90-day Complication Grade analysis (n=45). Abbreviations: SMI, Skeletal Muscle Index, PG-SGA, Patient Generated Subjective Global Assessment; LOS, Length of Hospital Stay

In this cohort, the majority of events involved complications of the GI system including emesis, diarrhea, constipation, and ileus. Urinary tract infection (UTI) was also among the top most prevalent events (n=13) (Table 6).

Table 6. Most Common Adverse Events within 90-days of Radical Cystectomy

Event	n (% total adverse events)
Emesis	14 (9.4)
UTI	13 (8.7)
Diarrhea	11 (7.4)
Constipation	9 (6.0)
Ileus	8 (5.4)
Anemia Requiring Transfusion	8 (5.4)
Dehydration	8 (5.4)
Hypotension	7 (4.7)
Sepsis	6 (4.0)
Renal Failure	5 (4.0)

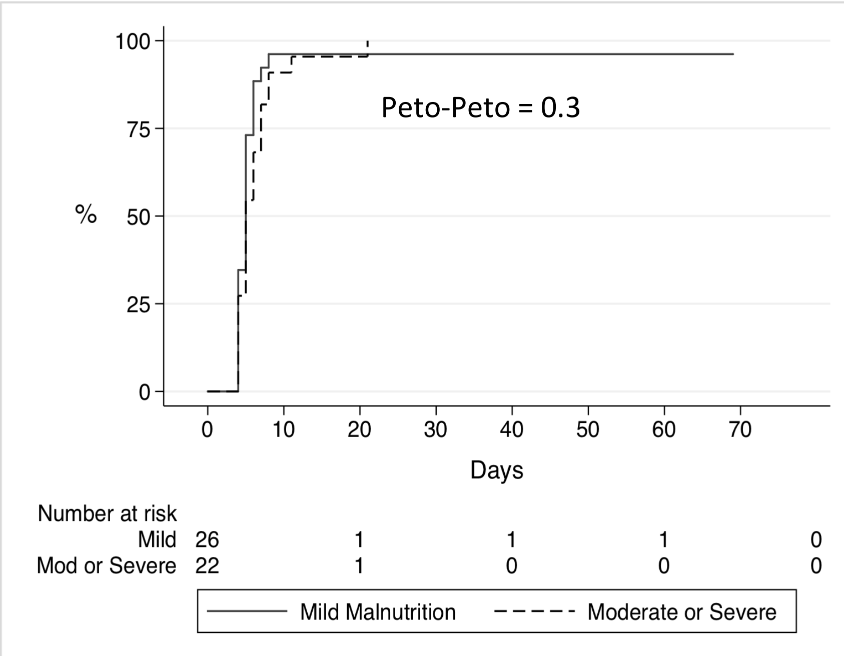
Distribution of the top ten most common adverse events within 90-days of radical cystectomy for 48 subjects. Multiple occurrences on the same adverse event were only accounted for once and events occurring intraoperatively were excluded. Any adverse events experienced by patients who may have been lost to follow up were still included in this distribution.

Clinical Outcomes by Malnutrition Grade

Time to discharge did not differ significantly among mild and moderate/severe malnutrition groups (Figure 5) and both groups had a median time to discharge of five days. We analyzed the time to discharge among the two groups using a Kaplan Meier survival analysis. We used the Peto-Peto test for significant instead of a Cox regression method to test for significance (p=0.3) as this test places greater emphasis on earlier events on the survival curve.

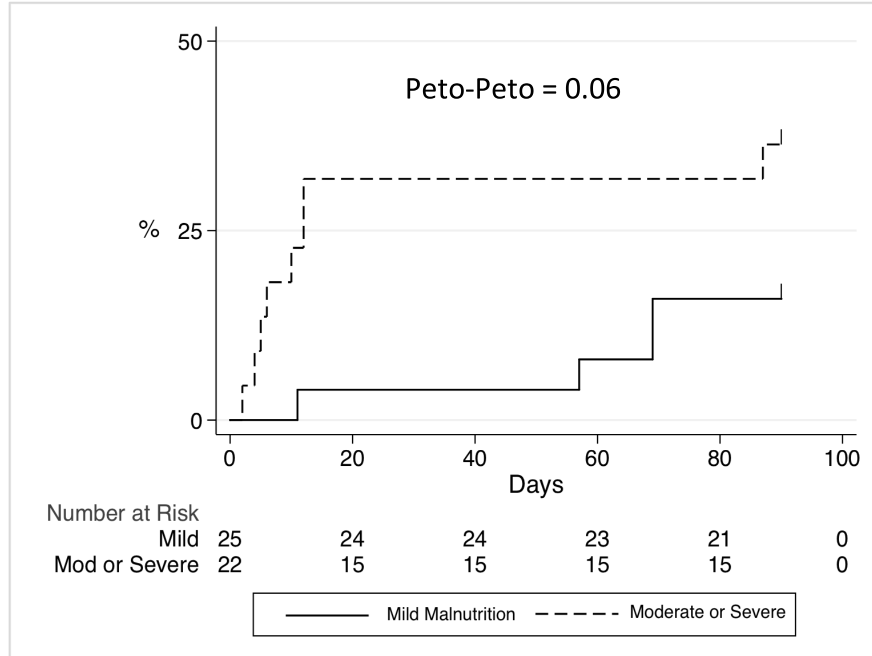
Similar to time to discharge, readmission rate was analyzed among the two malnutrition groups using a Kaplan Meier survival analysis and Peto-Peto test for significance. Incidence of 90-day readmission did not differ significantly among mild and moderate/severe malnutrition groups (p=0.06) (Figure 6). However, the difference among groups did approach significance and the incidence of readmission was greater in the moderate/severe group compared to the mild group in 30-day (7 vs. 1) and 90-day periods (8 vs. 4).

Figure 5. Time to Discharge



F5. Time to discharge measured by number of days from surgery date to discharge among subjects with mild to moderate/severe malnutrition (n=48). Malnutrition grade was captured by the preoperative Patient Generated Subjective Global Assessment (PG-SGA). Kaplan-Meier statistic was utilized to determine differences among mild and moderate/severe groups in relation to time to discharge. Peto-Peto test p=0.3. An α level of <0.05 was considered significant for all statistical tests.

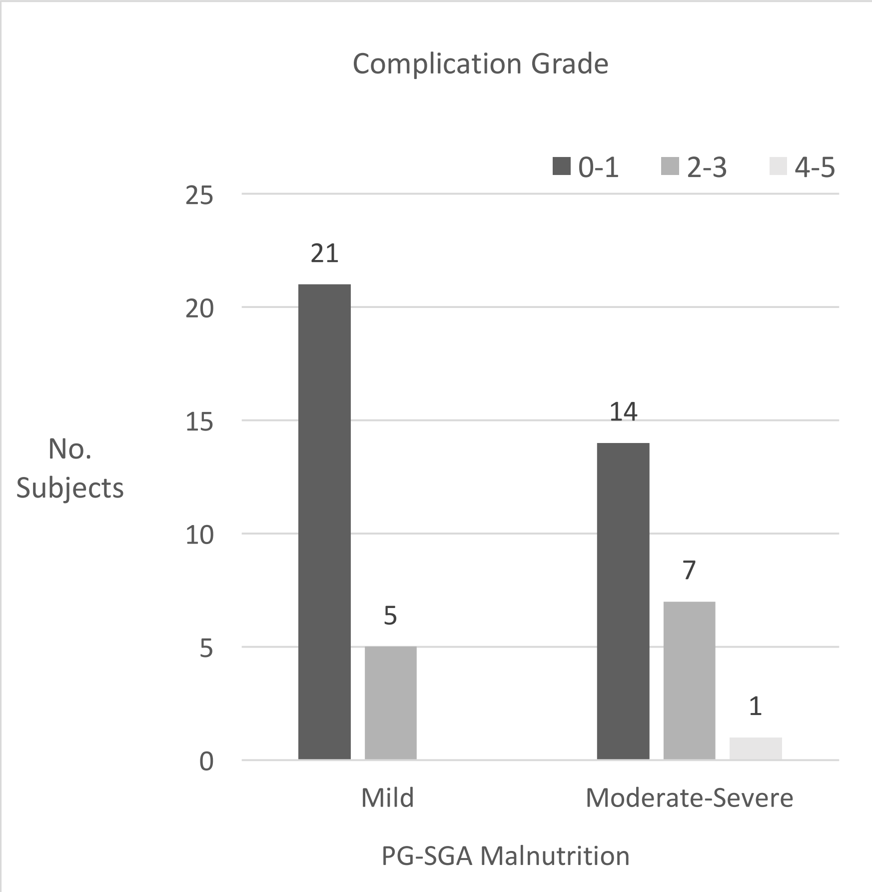
Figure 6. Cumulative Incidence of Readmission



F6. Cumulative incidence of hospital readmission from 90-days of surgery date in subjects with mild to moderate/severe malnutrition (n=47). Malnutrition grade was captured by the preoperative Patient Generated Subjective Global Assessment (PG-SGA). Kaplan-Meier statistic was utilized to determine differences among mild and moderate/severe groups in relation to incidence of readmission. Peto-Peto test p=0.06. An α level of <0.05 was considered statistically significant for all statistical tests.

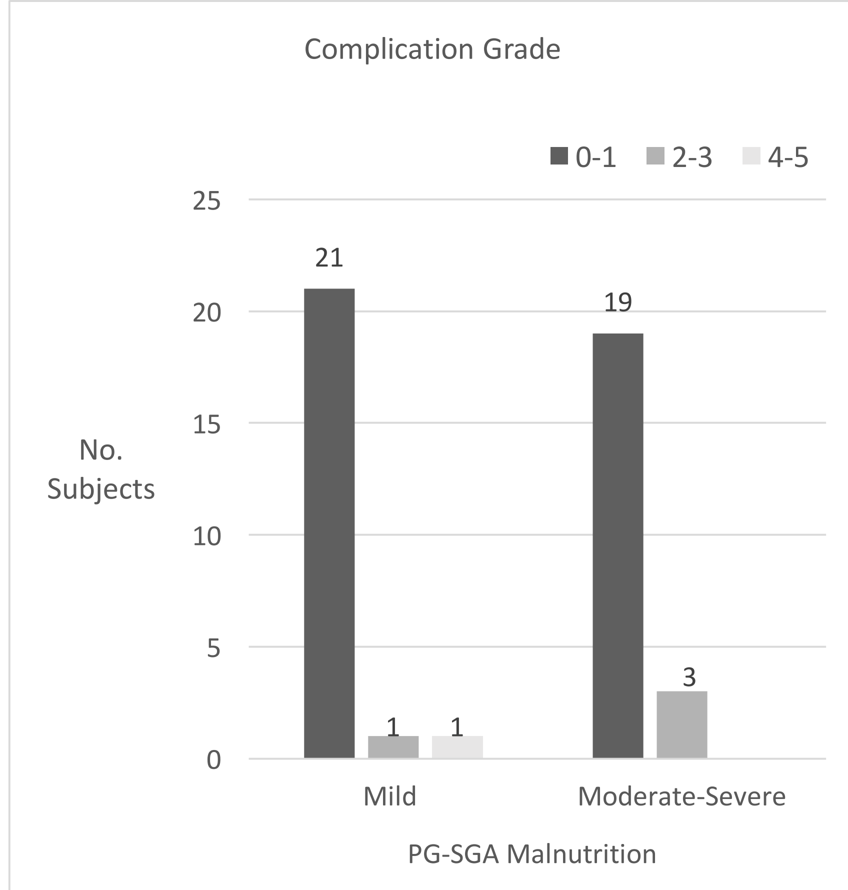
During the study period, almost 25% of patients presented with a complication grades of 2-3 and one patient died within 30 days of surgery. For 90-day complication grades, <10% of patients presented with complication grades of 2-3 and one patient had a grade of 4 (lasting disability). Malnutrition grade did not have a significant effect on MSK complication grades for 30-day (n=48) or 90-day MSK grades (n=45) (Figures 7, 8). Three (3) subjects were lost to follow up for 90-day analyses. A subject with moderate/severe malnutrition was just as likely as a subject with mild malnutrition to have a greater 30-day MSK grade (Mann-Whitney; 59%, 95% CI: 46—72%, p=0.2). Similar results with 90-day MSK grade analyses (52%, 95% CI: 43—62%, p=0.6).

Figure 7. Malnutrition and 30-day Complications



F7. Subject distribution of Memorial Sloan Kettering Cancer complication grades within 30-days of radical cystectomy surgery among mild and moderate/severe malnutrition groups (n=48). Malnutrition grade was captured by the preoperative Patient Generated Subjective Global Assessment (PG-SGA). Mann-Whitney test between malnutrition groups; $p>0.05$. An α level of < 0.05 was considered significant for all statistical tests. Abbreviations: Patient Generated Subjective Global Assessment (PG-SGA).

Figure 8. Malnutrition and 90-day Complications



F8. Subject distribution of Memorial Sloan Kettering Cancer complication grades within 90-days of radical cystectomy surgery of subjects among mild and moderate/severe malnutrition groups (n=45). Malnutrition grade was captured by the preoperative Patient Generated Subjective Global Assessment (PG-SGA). Mann-Whitney test between malnutrition groups *$p>0.05$.* An α level of < 0.05 was considered significant for all statistical tests.

Discussion

Radical cystectomy is associated with high morbidity and complication and readmission rates. Predictive physiological markers such as sarcopenia and malnutrition may prove useful in stratifying patient complications, LOS, and readmission rates. These markers are still novel and it is unclear whether they could be used together or as proxy for one another to assess patient readiness for major abdominal surgery. Therefore, we evaluated SMI index in men and women before and after RC with various ages, BMIs, and comorbidities.

In the current study, we did not differentiate subjects based on the presence of or lack of presence of sarcopenia as available cutoffs are based on study populations that may not be generalizable to other populations.[25] We opted instead to calculate a relative score for SMI to determine patient score in relation to a median score for each sex. Overall, malnutrition stage did not correlate with an increased or decreased relative SMI score during the pre-op time frame. Although only marginally significant, males diagnosed with a greater severity of malnutrition did have a decreased relative pre-op SMI compared to mildly malnourished subjects (p=0.07). This trend was not observed in females. In corroboration with the current study, Sheean et al. used L3 images to examine prevalence of sarcopenia in ICU patients (n=56) and found it was not associated with SGA rankings after controlling for age.[38] Researchers concluded that since the SGA was developed by Baker et al. more than thirty years prior based on a normal weight population it may no longer be reliable in assessing for malnutrition and severe muscle wasting in critically ill sarcopenic obese individuals.

In the current study, there was a negative change in mean SMI from baseline meaning SMI decreased by about 2 units from pre-op scan to post-op scan. The negative trend was more pronounced in males than females in which the mean change in SMI was -0.4 units. Contrary to our hypothesis, subjects in the moderate-severe malnutrition group had a more positive change in SMI and thus experienced less of a decrease in SMI during the surgical treatment period. A Japanese retrospective analysis of RC patients (n=89) found the cross-sectional area at the level of L3 of the psoas major muscle showed a significant deterioration at one and three months after RC, with a return to baseline values from six to 24 months.[39] However, SMI did not significantly change postoperatively. We did not measure the psoas major muscle group thus future studies could include skeletal muscle measures of the psoas in addition to entire core muscle group at various time points during post-op recovery period to determine individual rates of skeletal muscle resiliency.

In the current study, subjects diagnosed with more severe malnutrition experienced an increased readmission rate within 90 days, however, it was only a marginally significant increase in readmission rate compared to subjects diagnosed with mild malnutrition (p=0.06). Thus, we are not certain on the clinical significance of this finding. Most readmissions occurred within the first 20 days of surgery, thus, there was a strong divergence between nutrition groups earlier in the survival curve so our results may have been different if we limited the readmission to just two to four weeks after surgery. In addition to readmission rate, we also tracked hospital LOS. The severely malnourished subjects did not have a greater LOS and the median LOS was five days for both groups.

Previously published reports of retrospective studies conflict with our results and study conclusions are still mixed regarding the PG-SGA as a predictor of hospital LOS and readmission. In a retrospective single institution study of cancer patients >18 years of age (n=71), Bauer et al. observed a significant correlation between PG-SGA score and LOS (r=0.3,p=0.034).[17] However, upon regression analysis they determined that none of the variables, age, diagnosis, weight loss percentage, BMI, or PG-SGA score, were predictors of LOS within 30 days of discharge. The final model for predictors of LOS included PG-SGA score (F(1,63)=3.586, P=0.06) which accounted for 5% of the variation in LOS. However, our cohorts varied considerably. The cohort in the Bauer et al. study included hospitalized patients (surgical status unknown) with an average age of 57.6 (18-92 years), relatively equal sex distribution and various cancer types, lymphoma being the most common. Furthermore, in a prospective cohort study of 1022 acute care and surgical patients ≥ 18 years old, Jeejeeboy and colleagues observed that after controlling for age, sex, and diagnosis, a malnutrition score of severe was an independent predictor of LOS. Subjects with a severe malnutrition score were more than twice as likely to have an increased LOS compared to subjects with mild and moderate malnutrition (OR: 2.19; 95% CI: 1.28— 3.75).[36] Subjects with a severe malnutrition score were also more than twice as a likely to be readmitted within 30 days compared to mild and moderate groups.[36] This study population also varies considerably with our study in terms of age of subjects although they did include patients undergoing major abdominal surgery.

Furthermore, Lim et al. assessed nutrition status using the SGA in a prospective cohort study of hospitalized patients including 22 urology patients in Singapore (n=818).[37] Lim et al. observed that independent of gender, age, race, and diagnosis, malnourished patients (moderate or severe) had longer hospital stays compared to well-nourished patients (6.9 ± 7.3 days vs. 4.6 ± 5.6 days, $p < 0.001$) and were almost twice as likely to be readmitted within 15 days (adjusted RR = 1.9, 95% CI: 1.1—3.2, $p = 0.025$). Lim et al. also observed malnourished patients were more likely to be male and older. In comparison to our study, the median age of moderate/severely malnourished patients (72.5 years) was greater than mildly malnourished subjects (65 years) in our study, we observed that the proportion of males and females were relatively equal in the moderate-severe malnutrition group. Lim et al. mentioned that the readmission rate may have been underestimated in some subjects, as they were unable to monitor patients re-admitted to other hospitals. One merit of our study was the ability of researchers to access CareEverywhere, an exchange network that allows health care professionals to electronically share patient medical information within certain EMR academic medical systems. In addition to other communication records within the EMR system, the exchange network allowed researchers to confirm subject adverse events, readmissions, and other clinical data at various institutions.

Using a validated assessment of complications after surgery, the MSK complication grading system, we did not find that malnutrition status affected the severity of complication grade (1-5). However, the PG-SGA may have prognostic value in surgical cohorts. In a 2016 prospective cohort study of elective surgical patients (n=60), Harter et al. observed that patients with moderate/severe malnutrition were much more likely to have a severe surgical complication (p=0.001).[40] Severe surgical complications were considered a Clavien-Dindo score of 3-5. In our study, we used an adaptation of the Clavien-Dindo that is almost identical however, we did not execute separate analyses for severe complications.

Perhaps the most significant limitation of this study is the small sample size and the homogeneity of subject demographics, which drastically reduces the report's ability to provide reliable, meaningful and generalizable results to other cohorts. The limitations of the current report also include selection bias inherent in the study design and patient recruitment protocol. During the study time frame, not all bladder cancer patients undergoing RC were consistently referred to the RDN for malnutrition screening and assessment by the surgical team prior to surgery. Also, several patients were excluded that did not visit an RDN for a pre-op visit and did not complete a PG-SGA. Furthermore, the PG-SGA assessment and other clinical characteristic assessments such as age-adjusted CCI and complication grading were measured patients during various times of their pre-op surgical course. Other studies have collected malnutrition assessment data during particular perioperative time windows and tested for malnutrition with a second examiner to control for interrater reliability.[25,40] It is also important to note that there was variability in the timing of the CT scans during the treatment period, which may overestimate or underestimate skeletal muscle resiliency in particular subjects specifically in the post-op healing window. Thus, prospective randomized controlled trials are needed to clearly and reliability assess for the presence of malnutrition and its severity as well as SMI during particular time periods within the treatment period.

Despite these limitations, this study demonstrated the feasibility of collecting both malnutrition characteristics and SMI as a more comprehensive assessment of patient's baseline nutrition status prior to surgery. The PG-SGA is a malnutrition tool recognized by AND and ASPEN as a reliable tool associated with longer hospital LOS, readmission rate, and post-op complications.

PG-SGA also includes a functional status component that takes patient changes in activity and functional status into account. Although functional status was not extrapolated from the assessment, it contributes to the validation of the assessment of sarcopenia. Furthermore, one single examiner determined the severity of malnutrition via the PG-SGA assessment tool and the MSK complication grade, thus minimizing interrater variability. The current study also demonstrates the feasibility of the collection of SMI and nutrition indices in conjunction in order to estimate the patient's functional, physical, and nutrition status during surgical treatment.

SMI, as a surrogate for sarcopenia, must continue to be standardized and validated in various surgical cohorts and patient demographics. Patients with bladder cancer frequently undergo CT imaging for diagnostic purposes, which presents a novel opportunity for assessment of body composition. In future studies, it is important to consider that within current definitions of sarcopenia, functional status or strength assessment using handgrip strength or walk speed tests should be included in the assessment of sarcopenia [5]. Improving patient care through assessment of patient readiness for surgery and need for preoperative nutritional intervention is of high priority but the first step is to agree upon validated diagnostic tools in clinical practice.

References

1. Ahmadi H, Terjimanian M, Chernin AS, et al. MP60-13 PSOAS MUSCLE MASS AS A PREDICTOR OF SURVIVAL IN PATIENTS WHO UNDERGO RADICAL CYSTECTOMY. *The Journal of Urology.* 2014;191(4, Supplement):e637.
2. Smith AB, Deal AM, Yu H, et al. Sarcopenia as a Predictor of Complications and Survival Following Radical Cystectomy. *The Journal of Urology.* 2014;191(6):1714-1720.
3. Psutka SP, Carrasco A, Schmit GD, et al. Sarcopenia in patients with bladder cancer undergoing radical cystectomy: impact on cancer-specific and all-cause mortality. *Cancer.* 2014;120(18):2910-2918.
4. White JV, Guenter P, Jensen G, Malone A, Schofield M. Consensus Statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: Characteristics Recommended for the Identification and Documentation of Adult Malnutrition (Undernutrition). *Journal of the Academy of Nutrition and Dietetics.* 2012;112(5):730-738.
5. Muscaritoli M, Anker SD, Argilés J, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: Joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clinical Nutrition.* 2010;29(2):154-159.
6. Society AC. Key Statistics for Bladder Cancer. 2017; https://www.cancer.org/cancer/bladder-cancer/about/key-statistics.html - written_by. Accessed May 8, 2017.
7. Araújo dos Santos C dOBRC, Queiroz Ribeiro A, Lanes Ribeiro Rde C. . Patient-generated subjective global assessment and classic anthropometry: comparison between methods in detection of malnutrition among elderly with cancer. . *Hosp.* 2015;31(1):384-392.
8. Shariat SF, Milowsky M, Droller MJ. Bladder cancer in the elderly. *Urologic Oncology: Seminars and Original Investigations.* 2009;27(6):653-667.
9. Chappidi MR, Kates M, Stimson CJ, Johnson MH, Pierorazio PM, Bivalacqua TJ. Causes, Timing, Hospital Costs, and Perioperative Outcomes Of Index vs. Non-Index Hospital Readmissions Following Radical Cystectomy: Implications For Regionalization of Care. *The Journal of Urology.* 2017;197(2):296-301.
10. Svatek RS, Fisher MB, Matin SF, et al. Risk factor analysis in a contemporary cystectomy cohort using standardized reporting methodology and adverse event criteria. *J Urol.* 2010;183(3):929-934.
11. Shabsigh A, Korets R, Vora KC, et al. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. *Eur Urol.* 2009;55(1):164-174.
12. Hautmann RE, Gschwend JE, de Petriconi RC, Kron M, Volkmer BG. Cystectomy for transitional cell carcinoma of the bladder: results of a surgery only series in the neobladder era. *J Urol.* 2006;176(2):486-492; discussion 491-482.
13. Quek ML, Stein JP, Daneshmand S, et al. A Critical Analysis of Perioperative Mortality From Radical Cystectomy. *The Journal of Urology.* 2006;175(3):886-890.

14. Fielding RA, Vellas B, Evans WJ, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *J Am Med Dir Assoc.* 2011;12(4):249-256.
15. Morley JE, Abbatecola AM, Argiles JM, et al. Sarcopenia with limited mobility: an international consensus. *J Am Med Dir Assoc.* 2011;12(6):403-409.
16. Rennie MJ, Selby A, Atherton P, et al. Facts, noise and wishful thinking: muscle protein turnover in aging and human disuse atrophy. *Scand J Med Sci Sports.* 2010;20(1):5-9.
17. Bauer J, Capra S, Ferguson M. Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. *European Journal of Clinical Nutrition.* 2002;56(8):779-785.
18. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol.* 1998;147(8):755-763.
19. English KL, Paddon-Jones D. Protecting muscle mass and function in older adults during bed rest. *Curr Opin Clin Nutr Metab Care.* 2010;13(1):34-39.
20. Paddon-Jones D. Interplay of stress and physical inactivity on muscle loss: Nutritional countermeasures. *J Nutr.* 2006;136(8):2123-2126.
21. Bauer JM, Sieber CC. Sarcopenia and frailty: a clinician's controversial point of view. *Exp Gerontol.* 2008;43(7):674-678.
22. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing.* 2010;39(4):412-423.
23. Morley JE, Baumgartner RN, Roubenoff R, Mayer J, Nair KS. Sarcopenia. *Journal of Laboratory and Clinical Medicine.* 2001;137(4):231-243.
24. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc.* 2002;50(5):889-896.
25. Prado CMM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *The Lancet Oncology.* 2008;9(7):629-635.
26. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab.* 2008;33(5):997-1006.
27. Hasselager R, Gogenur I. Core muscle size assessed by perioperative abdominal CT scan is related to mortality, postoperative complications, and hospitalization after major abdominal surgery: a systematic review. *Langenbecks Arch Surg.* 2014;399(3):287-295.
28. Bozzetti F, Mariani L, Lo Vullo S, et al. The nutritional risk in oncology: a study of 1,453 cancer outpatients. *Support Care Cancer.* 2012;20(8):1919-1928.
29. Teitelbaum D, Guenter P, Howell WH, Kochevar ME, Roth J, Seidner DL. Definition of Terms, Style, and Conventions Used in A.S.P.E.N. Guidelines and Standards. *Nutrition in Clinical Practice.* 2005;20(2):281-285.
30. Gillis C, Nguyen TH, Liberman AS, Carli F. Nutrition adequacy in enhanced recovery after surgery: a single academic center experience. *Nutr Clin Pract.* 2015;30(3):414-419.

31. Hand RK, Murphy WJ, Field LB, et al. Validation of the Academy/A.S.P.E.N. Malnutrition Clinical Characteristics. *J Acad Nutr Diet.* 2016;116(5):856-864.
32. Burden S, Todd C, Hill J, Lal S. Pre-operative nutrition support in patients undergoing gastrointestinal surgery. *Cochrane Database Syst Rev.* 2012;11:Cd008879.
33. Braga M, Gianotti L, Nespoli L, Radaelli G, Di Carlo V. Nutritional approach in malnourished surgical patients: a prospective randomized study. *Arch Surg.* 2002;137(2):174-180.
34. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. *Nutrition.* 1996;12(1 Suppl):S15-19.
35. Guerra RS, Fonseca I, Pichel F, Restivo MT, Amaral TF. Usefulness of six diagnostic and screening measures for undernutrition in predicting length of hospital stay: a comparative analysis. *J Acad Nutr Diet.* 2015;115(6):927-938.
36. Jeejeebhoy KN, Keller H, Gramlich L, et al. Nutritional assessment: comparison of clinical assessment and objective variables for the prediction of length of hospital stay and readmission. *Am J Clin Nutr.* 2015;101(5):956-965.
37. Lim SL, Ong KC, Chan YH, Loke WC, Ferguson M, Daniels L. Malnutrition and its impact on cost of hospitalization, length of stay, readmission and 3-year mortality. *Clin Nutr.* 2012;31(3):345-350.
38. Sheean PM, Peterson SJ, Perez SG, et al. The Prevalence of Sarcopenia in Patients With Respiratory Failure Classified as Normally Nourished Using Computed Tomography and Subjective Global Assessment. *Journal of Parenteral and Enteral Nutrition.* 2014;38(7):873-879.
39. Miyake M, Morizawa Y, Hori S, et al. Clinical impact of postoperative loss in psoas major muscle and nutrition index after radical cystectomy for patients with urothelial carcinoma of the bladder. *BMC Cancer.* 2017;17(1).
40. Harter J, Orlandi SP, Gonzalez MC. Nutritional and functional factors as prognostic of surgical cancer patients. *Support Care Cancer.* 2017.