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Impact of body size and body composition on bladder cancer outcomes: risk stratification and opportunity for novel interventions

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Abstract

Body size is emerging as a novel and clinically-relevant patient factor in bladder cancer research. Historically, a patient's body mass index (BMI) has been used as a proxy for obesity but it shows inconsistent associations with risk of developing the disease as well as with most clinical outcomes. More specific body composition features can be derived for patients using a variety of methods. To date, skeletal muscle measurements derived from pre-operative computed tomography scans have shown the most consistent associations with clinical outcomes. Importantly, skeletal muscle can potentially be modified through resistance training and/or nutritional interventions. Large scale studies that evaluate the prognostic impact of not only body composition features at baseline but also describe changes in body composition post-treatment are needed to move the field forward to ultimately improve clinical outcomes for bladder cancer patients.

Keywords

bladder cancer; obesity; body mass index; body composition; exercise; skeletal muscle; adiposity; sarcopenia

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Introduction

Bladder cancer is the tenth most common cancer worldwide and is categorized based on pathological depth of tumor invasion. Most bladder cancer patients are diagnosed with non-muscle invasive bladder cancer (NMIBC) which has the highest recurrence risk of any malignancy. Standard treatment consists of transurethral resection with intravesical immune- or chemotherapy, but a subset of patients progress to muscle-invasive bladder cancer (MIBC). Clinical management of MIBC patients include radical cystectomy with pelvic lymphadenectomy and urinary diversion as well as neoadjuvant or adjuvant chemotherapy. Unfortunately, MIBC patients experience substantial morbidity and mortality after cystectomy. Existing risk prediction models that estimate risk of recurrence, progression or survival have limited accuracy for the individual patient and rely primarily on clinicopathological variables[1]. Novel factors that improve risk stratification are needed. Emerging research suggests that body size constitutes a novel and clinically-relevant patient factor that potentially could be leveraged to refine risk prediction and be modified to improve clinical outcomes. The purpose of this commentary is to summarize what is known about body size (i.e., both body mass index (BMI) and body composition) in relation to bladder cancer risk and clinical outcomes, and to discuss future research directions.

Body size basics: moving beyond BMI

Historically, BMI (categorized as normal weight 18.5–25 kg/m^2, overweight 25–30 kg/m^2, and obese > 30 kg/m^2), has been used to represent obesity. On a population level, BMI is a good marker of overall body fat content but does not accurately reflect individual distribution of body fat (subcutaneous vs. visceral) or muscle mass which may have different biological effects[2,3]. More specific body size features can be derived from different sources such as computerized tomography (CT) scans, magnetic resonance imaging (MRIs), dual-energy absorptiometry (DEXA), and bioelectrical impedance analysis (BIA). The most applicable for bladder cancer research are CT scans, which are obtained for staging and surveillance purposes. CT scans taken at the level of the third lumbar vertebrae (L3) are linearly related to whole body total adipose tissue and skeletal muscle mass[4,5], and can be used to obtain both the cross-sectional area and the radiodensity of these tissues using established Hounsfield Units (HU) for each tissue type. Similar to BMI, the cross-sectional area variables can be divided by height in meters squared to derive the index for each (e.g., skeletal muscle index (SMI), visceral adipose tissue index (VATI) and subcutaneous adipose tissue index (SATI)). Radiodensity of muscle and adipose tissues can also be obtained but have not been widely studied in cancer. Table 1 presents common body composition variables that can be derived from CT images. As validated cut-points for high and low levels are lacking for most variables, many studies report study- and gender-specific distributions, making direct comparisons between studies challenging. Notably, low SMI alone is not synonymous with the term ‘sarcopenia’ which requires the addition of measures of strength, muscle performance, or physical performance for proper classification[6] or ‘cachexia’ which requires weight loss >5% or >2% in individuals with a BMI <20 kg/m^2 or sarcopenia[7]. Single muscle quantification (i.e., psoas) may not accurately represent overall skeletal muscle because it does not correlate with total skeletal area in cancer patients[8,9].

Despite these methodological issues, body composition features appear to be novel prognostic factors across several cancers, including bladder cancer.

Association of obesity defined by BMI with incidence and clinical outcomes

Associations between high BMI and *risk of developing* NMIBC and MIBC are not consistent across studies. Three prior meta-analyses each report about a 10% increased relative risk of developing bladder cancer[10–12], while a recent prospective cohort of over 800,000 men and women found that the positive association between high BMI and risk was limited to males, and to those with NMIBC[13]. With respect to *prognosis* among NMIBC patients, a recent meta-analysis of 31 studies and a study across 13 institutions (n=1,155) found that patients who were overweight or obese had a significantly increased risk of recurrence (HR 5.33; $p<0.001$) compared to patients who were classified as normal weight at diagnosis[14,15]. Results for progression to MIBC were conflicting between studies. In MIBC, compared to normal weight patients, those who were overweight or obese experience longer operative times, more blood loss, and higher rates of perioperative complications[16–18]. Although BMI is routinely measured as part of cancer care, it is widely acknowledged that BMI is a crude measure of body size that cannot delineate body composition features such as skeletal muscle, visceral adipose and subcutaneous adipose tissues[2]. Indeed, cancer patients with the same BMI can vary widely in their body composition features (Figure 1).

Association of body size features with clinical outcomes

Several retrospective studies have examined the relationship between body composition and bladder cancer outcomes. These studies focused largely on associations between SMI and clinical outcomes. There is limited assessment of adiposity (e.g., VATI, SATI) in relation to morbidity, mortality or systemic treatment response in bladder cancer.

Low skeletal muscle in surgically treated bladder cancer patients

A recent systematic review and meta-analysis of 12 retrospective studies by Hu, et al. [19] evaluated the association of CT-derived muscle features with oncologic outcomes in both surgically treated localized bladder (n=7 studies) and upper tract urothelial carcinoma (n=5 studies). Among localized bladder cancer patients treated with radical cystectomy (n=1,509), the overall prevalence of low SMI was 51.2% (ranging from 20–75%). Bladder cancer patients with low SMI experienced worse overall- (OS, HR 1.63, 95%CI 1.37–1.94) and cancer-specific survival (CSS, HR 1.73, 95%CI 1.35–2.21) compared to patients with high SMI.

Overall, studies evaluating the association of low pre-operative SMI in patients with localized bladder cancer treated with radical cystectomy suggest worse OS and CSS[3,20,21]. Mayr et al.[22] conducted the largest retrospective study to date. It included 500 patients who underwent radical cystectomy with a median follow-up of 22 months (IQR 10–45 months). Patients with low SMI experienced inferior 5-year OS (38.3% vs. 50.5%, p=0.002) and CSS (49.5% vs 62.3%, p=0.016). After adjusting for clinicopathologic variables including receipt of adjuvant chemotherapy and BMI, low SMI remained significantly associated with increased all-cause mortality.

Chemotherapy and radiation therapy

Several groups have evaluated the association of body composition with chemotherapy response and toxicity. Zargar et al. evaluated 60 patients that underwent neoadjuvant chemotherapy (NAC) followed by consolidative radical cystectomy. Evaluating pre- and post-NAC CT scans, the receipt of NAC was associated with a significant 4.9% decrease in psoas muscle volume (PMV) and 0.05% in BMI; however, there was no significant association between change in PMV and pathologic response, complications, readmission, or survival outcomes. NAC dose reduction/delay (n=11, 18%) was a predictor of PMV loss (p=0.047)[23]. Other retrospective studies have not found a significant association between pre-operative low SMI and median time to cystectomy, chemotherapy dose reduction, delay of chemotherapy administration, toxicity or pathologic response[20,24]. Less is known about patients treated with definitive chemoradiation therapy. Among 68 comorbid patients unfit for radical cystectomy or systemic chemotherapy who underwent transurethral resection of bladder tumor and radiation, 72% had low SMI. In this older cohort (median age 82), having low SMI and obesity was associated with worse CSS (HR 5.0, 95%CI 1.4–16.7)[25].

Perioperative outcomes

Radical cystectomy is associated with significant post-operative morbidity and mortality. Among 327 patients undergoing RC, Mayr et al. identified low SMI as an independent predictor of postoperative complications and 90-day mortality (OR 2.59, 95%CI 1.13–5.95), and Clavien-Dindo grade 4a-5 complications (p=0.003)[26]. Among 63 male patients, Saitoh-Maeda et al. demonstrated that low PMI (n=34) was associated with a longer post-operative length of stay and worse OS[27]. Albersheim, et al.[28] also found that low SMI (OR 0.94, 95%CI 0.90–0.98) and high total adipose tissue mass (OR 1.24, 95%CI 1.04–1.48) were independently associated with discharge to a facility after radical cystectomy among 136 patients. Several studies also suggest that weight loss in the perioperative period can be a poor prognostic marker. The two studies that evaluated weight loss prior to or after radical cystectomy without assessment of body composition, reported increased rates of postoperative complications[29] and poor survival[30]. Among 75 patients undergoing radical cystectomy, regardless of initial body weight, weight loss of ≥10% at one-month post-operatively was associated with decreased 5-year survival (p=0.038). Notably, by 2-months post-operatively patients had lost a mean of 17 pounds[30].

Potential mechanisms underlying the associations of body composition features with oncologic outcomes

Obesity, characterized by increased adiposity, is known to contribute to malignancy via metabolic, inflammatory, and hormonal mechanisms[31]. Adipose tissue is an active endocrine organ secreting adipokines (e.g., leptin, adiponectin) which preliminarily have been shown to be have direct effects on bladder cancer cells *in vitro*[32]. However, other components of body size such as muscle may also contribute to cancer biology. In the absence of malignancy, age-related muscle loss is associated with a state of subclinical systemic inflammation reflected by elevated circulating inflammatory biomarkers (e.g., C-reactive protein)[33,34]. Among patients with localized colorectal cancer, low SMI has been associated with elevated circulating neutrophil-to-lymphocyte ratio (marker of inflammation) and the

combination of these two factors doubles the risk of death[35]. Whether tumors induces muscle loss directly or, alternatively, whether low SMI is a marker for an environment that promotes tumor progression, is unclear.

Modifying body composition

The emerging evidence that low SMI is associated with adverse outcomes in bladder cancer provides a strong rationale to examine the efficacy of interventions to modify it. In non-cancer settings, there is a wealth of observational and randomized trial data demonstrating that exercise and/or diet interventions are associated with improvements in body size metrics[36]. Retrospective studies suggest that physical activity favorably impacts bladder cancer risk and survival outcomes[37]. To date, no prospective trials have evaluated the role of exercise or diet on bladder cancer survival outcomes, however pre-operative (pre-habilitation) exercise and dietary interventions have shown some promise in improving functional outcomes after surgery[38]. Insights into how body composition change with exercise/diet impact survival outcomes can be gleaned from research conducted in other solid malignancies.

Exercise and body size change: lessons learned from other cancers

Under the influence of exercise, muscle secretes myokines (e.g. myostatin, interleukin-6) which have been shown to have anti-inflammatory and immunoprotective effects[39]. Resistance training alone or in combination with aerobic exercise during cancer treatment has favorable effects on muscle mass (i.e. preservation or increase) among breast and prostate cancer survivors on hormone therapy[40], and breast cancer survivors undergoing chemotherapy[41,42]. Additionally, a meta-analysis among 14 studies evaluating resistance training[43] in breast and prostate cancer survivors while undergoing active neoadjuvant or adjuvant treatment reported a significant increase of muscle mass (0.85 kg, 95%CI 0.76–0.95) and decrease in body fat percentage (−1.38 kg, 95%CI −1.57−−1.19)[43]. Notably, significant effects favoring resistance training to promote increases in muscle mass and reductions in fat mass was observed among patients on adjuvant chemotherapy but not neoadjuvant chemotherapy[43]. Post-treatment, a systematic review of randomized and non-randomized controlled trials suggests resistance training may increase muscle mass in head and neck, breast, prostate, colorectal, lymphoma, and lung cancer survivors[44].

Nutrition and body composition change

Numerous trials have evaluated the effects of nutrition/diet interventions on body composition in various cancers, including bladder cancer. For instance, Dawson and colleagues[45] randomized prostate cancer patients on androgen deprivation therapy to one of four groups: protein supplementation coupled with resistance training, resistance training alone, protein supplementation alone, or sham exercise (control), for a 12-week intervention. Overall, the groups that participated in resistance training exhibited a significant increase in muscle mass (1.1 kg, 95%CI 0.4,1.8) and decrease in body fat percentage (−0.9%, 95%CI −1.8, −0.01); an added benefit of protein supplementation to facilitate a higher protein diet was not observed[45]. Madzima and colleagues[46] randomized breast cancer survivors to resistance training alone or protein supplementation (aimed to promote a higher protein diet) coupled with resistance training for 12-weeks and found that both groups increased muscle

mass and reduced fat mass[46]. Collectively, evidence supports resistance training during and after cancer treatment to promote preservation or increases in muscle mass. More evidence is needed to determine whether the addition of protein supplementation aimed at promoting a higher protein diet results in a synergistic effect on muscle mass among cancer survivors.

In a NMIBC trial (n=207), intravesical epirubicin alone or with a 12-month treatment with the probiotic *Lactobacillus Casei* showed an absolute ~15% decreased 3-year recurrence risk in the epirubicin and probiotic arm[47]. Another study found that broccoli sprout extract may help decrease recurrence risk but awaits validation in larger studies[48]. In the MIBC setting, Ritch, et al.,[49] evaluated the role of perioperative oral nutrition supplementation (Ensure®) or twice daily multivitamin (Member's Mark®) starting 3–4 weeks prior to radical cystectomy for MIBC and continuing for 4 weeks after surgery with a primary endpoint of 30-day hospital free days and secondary endpoints of hospital length of stay, complications, and readmissions. Notably, patients receiving nutritional supplementation had a stable prevalence of sarcopenia while in the multivitamin group there was a 20% increase in sarcopenia. These results suggest that nutritional supplementation alone in the perioperative setting may be useful to *preserve* muscle mass. The Southwestern Oncology Group (SWOG) currently has a phase III trial open to evaluate the role of immune-nutrition in the perioperative setting (SWOG1600, NCTN03757949) with a primary endpoint of 30-day post-operative complications based on strong preliminary data[50]. Pre-habilitation with exercise and nutritional interventions has also shown promise in improving functional outcomes for patients after cystectomy[38].

Conclusions and future directions

Existing risk prediction models that estimate risk of recurrence, progression or survival are based predominantly on clinicopathological variables and have limited predictive accuracy for the individual patient[1]. Integrating additional patient-related factors such as comorbidities to nomograms is an active area of research. Using SEER-medicare data, Williams, et al.[51] integrated clinicopathological, sociodemographic, and Charlson Comorbidity Index (CCI) variables to predict 3- and 5-year cancer-specific and all-cause mortality among patients undergoing RC, while Morgan et al. showed that low pre-operative serum albumin (reflection of nutritional status) and CCI significantly predicted 90-day survival among elderly patients undergoing RC[52]. Body composition features that are significantly associated with clinical outcomes and are independent of traditional clinicopathological variables and comorbidities may improve risk prediction but have yet to be explored.

Table 2 presents a summary of future investigations related to body composition that are needed in bladder cancer. The field should move beyond BMI when assessing the clinical impact of patient body size. Developing exercise and/or nutritional interventions that modify body composition features and actually improve clinical outcomes along the entire disease course are warranted. For example, future studies could examine how pre-habilitation affects peri-operative outcomes, or whether adjuvant interventions decrease the risk of cardiovascular mortality among survivors. Assessing body composition in the clinic and in research studies will be facilitated by the automated body composition programs that are

actively being developed[53]. In conclusion, body composition is emerging as a novel prognostic factor that could be leveraged to potentially improve care and survival of bladder cancer patients.

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Highlights

- BMI is an inadequate marker of a patient's body composition features such as skeletal muscle and adiposity.
- Modifiable host-factors (e.g., skeletal muscle quantity) may have important prognostic implications throughout a patient's disease course
- There is a need for well-designed exercise and nutrition interventions to improve peri-operative and long-term survival outcomes for patients with bladder cancer

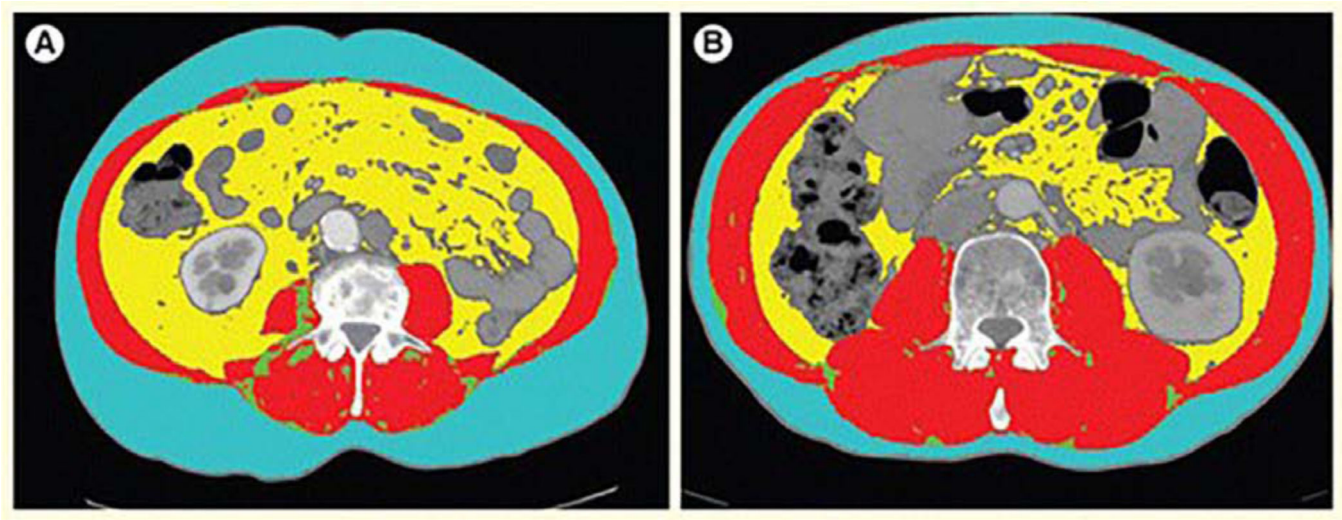

Figure 1.

CT scans from two cancer patients with the same BMI but very different body composition features. CT scans from two different RCC patients, A and B, who have the same BMI but different body composition features. The blue area is subcutaneous fat, the red is skeletal muscle, and the yellow is visceral fat. Patient A has more subcutaneous and visceral fat and far less skeletal muscle than patient B.”

Table 1.

Key body composition terms

Body Composition: Area and radiodensity of muscle and adipose tissue, which cannot be assessed using measures of weight and height, but can be precisely quantified using CT scans taken for staging or surveillance of bladder cancer patients
Skeletal Muscle Index (SMI): Cross-sectional area of muscle divided by height squared (i.e., amount of muscle tissue)
Skeletal Muscle Radiodensity (SMD): Reflects fatty infiltration to the muscle (i.e., density of muscle tissue)
Visceral & Subcutaneous Adipose Tissue Index (VAT Index & SAT Index): Cross-sectional area of each adipose tissue divided by height squared (i.e., amount of adipose tissue)
Visceral & Subcutaneous Adipose Tissue Density (VAT Radiodensity & SAT Radiodensity): Reflects lipid content of adipocytes in each tissue (i.e., density of adipose tissue)

Table 2.

Bladder cancer research priorities related to body composition

Identify body composition features (alone and in combination) that are associated with clinical outcomes in NMIBC and MIBC patients
Identify mechanisms underlying the associations between body composition and clinical outcomes • Characterize local and systemic inflammatory, metabolic and hormonal differences by body size features
Characterize relationship between performance status, strength, and muscle and adipose tissue quantity throughout the disease course
Describe changes in body composition over the disease course (e.g, baseline preoperative vs. 6- and 12-months post-treatment)
Develop exercise and nutritional interventions to improve bladder cancer outcomes • Among patients with NMIBC, can these interventions decrease the risk of recurrence and progression? • Among patients with MIBC, can interventions improve perioperative, overall- and cancer-specific survival outcomes
Develop nutritional and exercise interventions to improve health-related quality of life and prevent long-term sequalae of bladder cancer treatments such as chronic kidney disease and cardiovascular disease