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EUO Collaborative Review – Bladder Cancer

Staging the Host: Personalizing Risk Assessment for Radical Cystectomy Patients

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Abstract

Context: Perioperative and long-term functional and oncologic outcomes following radical cystectomy (RC) for localized bladder cancer remain unchanged despite advances in technique and perioperative management, as well as neoadjuvant and adjuvant therapy. Accurate assessment of a patient's perioperative risk is critical to inform preoperative counseling and determine a patient's fitness for RC.

Objective: To review and synthesize conventional and novel objective patient-specific risk assessment tools that may be incorporated into clinical practice for perioperative risk prognostication with respect to both postoperative complications and long-term oncologic outcomes, patient counseling, and decision-making when RC is being considered.

Evidence acquisition: A collaborative review was performed to synthesize currently available evidence on comorbidity, age, body composition, nutrition, frailty, and geriatric assessments for patients undergoing RC.

Evidence synthesis: Current guidelines recommend that pre-RC risk assessment should take into account age, performance status, and comorbidity. However, conventional comorbidity indices perform inconsistently in accurate assessment of the risk of perioperative complications, prolonged rehabilitation, and long-term oncologic outcomes. Novel metrics including standardized assessments of dependency, comorbidity severity, sarcopenia, malnutrition, physical and cognitive frailty, and comprehensive geriatric assessments may offer more precise estimates of physiologic age and relative vulnerability to adverse outcomes following RC.

Conclusions: Perioperative risk assessment before RC should incorporate objective measures of physiologic age, physical function, nutrition, lean muscularity, and frailty. The use of standardized multidimensional instruments should be encouraged for patients undergoing consideration for RC to identify potentially modifiable risk factors that can be targeted with prehabilitation interventions. Future work is needed to validate the performance of these metrics with respect to predicting perioperative complications and oncologic outcomes and to define and assess the effectiveness of specific prehabilitation interventions to optimize patients before surgery.

Patient summary: We review several metrics that doctors can use to measure the risks associated with bladder removal, a major surgical procedure. Moving beyond evaluating a patient's age, the burden of other health problems, and surgeon intuition, these tools may be used to counsel patients regarding their surgical risk, to predict oncologic outcomes, and to help identify potential interventions to improve surgical readiness.

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1. Introduction

Radical cystectomy (RC) with pelvic lymphadenectomy and urinary diversion represents an integral component in the management of patients with muscle-invasive bladder cancer (MIBC) and high-risk non–muscle-invasive bladder cancer. Unfortunately, despite increased adoption of neoadjuvant systemic therapy [1], the utilization of enhanced recovery after surgery protocols, and incorporation of minimally invasive surgical approaches, perioperative outcomes following RC [2,3] and post-RC survival rates have remained largely unchanged [4]. Indeed, contemporary series from high-volume centers report 5-yr overall survival (OS) rates of 42–58% [5,6], 90-d mortality estimates of 5–15% [7–9], and death within the index hospitalization of approximately 2–3% [10,11]. Furthermore, published complication rates range from 25% to over 80%, with major complications occurring in approximately one-third of cases [11–13]. Moreover, between 16% and 27% of RC patients cannot be discharged to their home after surgery, and require transitional care placement for continued rehabilitation [10]. Readmissions occur for nearly 40% of patients discharged after RC, of whom 26% require intensive care admission.

Although tumor-specific prognostic factors such as stage, grade, and margin status are well delineated [6,14], accurate prediction of a patient's ability to tolerate a major surgical intervention—effectively, "staging the host"—has proven much more challenging. Existing studies show inconsistent associations between adverse surgical outcomes and patient factors such as age, comorbidity, and performance status [15,16]. In the absence of established risk stratification tools, patient fitness is commonly primarily deduced from the treating surgeon's impression based on a standard history and physical examination; the so-called "eyeball test". However, such subjective assessments are challenging to quantify, validate, and reproduce. A knowledge gap therefore exists with respect to the comprehensive personalized risk stratification for a patient being considered for RC in the clinical setting. Furthermore, there remains a need for simple, accessible measures of comorbidity and perioperative risk that can be used in research and clinical practice. Therefore, our objective was to review and synthesize both conventional and novel patient-specific risk factors that can be incorporated into clinical practice for preoperative risk assessment, patient counseling, and decision-making when RC is being considered.

2. Evidence acquisition

A collaborative review of English-language articles on defining perioperative patient-specific risk factors for RC patients was undertaken. To identify eligible studies, a search of the MEDLINE electronic database was carried out from its inception to February 2018. MEDLINE search terms are listed in Supplementary Table 1. The literature search was expanded to include risk assessment metrics and schema as well as guidelines defined in other disciplines with relevance for the RC population (nutritional recommendations for cancer patients, guidelines for the management of geriatric cancer patients). To add context to the available study data, evidence around aging, comorbidity, body composition, obesity, malnutrition, frailty, and geriatric assessments are presented. We evaluated links to related articles and citations in the articles included and assessed recent relevant systematic reviews. The articles that provided the highest level of evidence were evaluated and selected according to the clinical judgment and expertise of the authors. Given that risk stratification according to the metrics discussed in this review is a rapidly evolving field and that the objective of this review was to evaluate novel risk stratification metrics, no formal statistical meta-analysis was possible, and a narrative synthesis of these data was therefore undertaken. It is also of note that the majority of the studies identified for the purpose of this review are based on retrospective and administrative data, with the paucity of level 1 evidence highlighting the need to further assess the associations described here in prospective studies and clinical trials.

3. Evidence synthesis

3.1. *Conventional assessments of comorbidity, function, and surgical risk*

Patients with MIBC often have other relevant medical conditions that mandate consideration during evaluation. For example, using administrative data from a large regional health network assessing 390 179 patients for the prevalence of 48 chronic conditions, Garg et al. [17] observed that bladder cancer patients have a median of eight chronic comorbid conditions, compared to a median of four in the general population. These existing conditions may in turn impact the care of patients with MIBC through direct association with noncancer mortality risk, and thereby influence treatment choice. For those undergoing RC, comorbidity burden can increase the complexity of perioperative management and the risks of complications and prolonged rehabilitation [18,19].

The interaction between comorbidity and perioperative and oncologic outcomes in bladder cancer is well recognized. The European Association of Urology (EAU) and American Urological Association (AUA) guidelines for MIBC recommend that a patient's treatment plan should account for comorbidity burden [2,20]. However, substantial variation exists in how comorbidity is quantified, and uncertainty persists regarding how an individual's comorbidity profile may impact perioperative risk and long-term outcomes

To date, considerable attention has been directed toward the interaction between single comorbid states and RC outcomes [18,21,22]. For example, Faiena et al. [23] evaluated the association between uncontrolled diabetes mellitus (DM) and morbidity following RC in a population-based sample, and noted that postoperative complications occurred in 72% of patients with uncontrolled DM, 51% of patients with controlled DM, and 52% of patients without DM. Uncontrolled DM is associated with prolonged hospital stay [23], while chronic kidney disease [24–26], severe liver disease [26], heart disease [8,27], and pulmonary disease [8] have likewise been found to be independently associated with early post-RC morbidity and mortality.

More recently, comorbidity indices, which are aggregate assessments of existing conditions, have been increasingly used to quantify comorbidity burden. The indices most commonly used include the Charlson comorbidity index (CCI) [28], which assesses 16 chronic illnesses with or without age-adjusted risk stratification, and the Elixhauser index (EI), a quantification of 30 comorbidities [29]. Although commonly used, reported associations between these indices and post-RC outcomes are inconsistent. For example, a study using Surveillance, Epidemiology and End Results data revealed that increasing CCI was independently associated with 90-d mortality: patients with CCI scores of 0, 1, 2, and ≥3 had 90-d mortality rates of 6.3%, 10.3%, 12.6%, and 15.9%, respectively [7]. Conversely, in a retrospective series from the Mayo Clinic, Boorjian et al. [6] found that CCI was not associated with 90-d mortality but did note an association between CCI and 5-yr all-cause mortality (ACM), while Koppie et al. [30] reported an association between CCI and noncancer mortality, but not cancer-specific mortality (CSM). Meanwhile, using the EI, Nayak and colleagues [10] observed that the risk of mortality during the index hospitalization, length of stay, a need for acute rehabilitation, and readmission rates increased with the number of comorbid conditions. This lack of consistency highlights a potential limitation of all such “comorbidity count” assessments, which is that they lack granularity with respect to disease severity and their impact on a patient’s overall function.

Other conventional risk assessment metrics include the American Society of Anesthesiology (ASA) score, which accounts for overall health and severity of concurrent systemic disease and was developed to prognosticate risk of mortality following surgery [31], and the Eastern Cooperative Oncology Group performance status (ECOG-PS) [32], a functional assessment that reflects relative independence versus dependence and overall daily function. When the accuracy of the CCI, EI, ASA score, and ECOG-PS was compared for the prediction of 90-d and 5-yr overall mortality and CSM among RC patients, Boorjian et al. [6] observed that the ASA score had the greatest relative predictive value for 90-d mortality, while CCI inclusion was most relevant for 5-yr CSM [6].

To increase the relevance of comorbidity assessment to bladder cancer patients, two RC-specific comorbidity indices have been developed. Dell’Oglio and colleagues [8] reviewed the relative prognostic value of the 17 comorbid conditions incorporated in the CCI, and observed that only five were independently associated with 90-d mortality after RC: congestive heart failure and cerebrovascular, rheumatologic, renal, and chronic pulmonary disease. Froehner and colleagues [33] generated a bladder CSM index for 10-yr noncancer mortality as an outcome, incorporating age, angina pectoris, chronic lung disease, DM, smoking, and ASA score; the index outperformed the age-adjusted CCI in terms of 10-yr competing mortality predictions.

Nevertheless, as concluded by a large systematic review of the comparative performance of available comorbidity indices [15], the performance of a given comorbidity metric is related to both the patient group under assessment and the outcome of interest. This point is illustrated in Table 1, which demonstrates the variable performance of the different comorbidity metrics across different outcomes and different patient cohorts in multivariable models. To illustrate, the CCI was developed among 608 general medical patients for the goal of predicting 10-yr overall survival in chronically ill patients [28], while the ECOG-PS was originally developed from a review of patients with various cancers to evaluate the likelihood of a patient’s ability to survive chemotherapy [32].

At present, no guideline recommends a single summary assessment of comorbidity and further evaluation in prospective cohorts and clinical trials is required to establish the optimal comorbidity metric for specific outcomes of interest. However, the importance of assessing a patient’s burden of competing comorbidities cannot be understated for risk stratification of patients considering RC in perioperative assessment. Moreover, the use of these measures in advance of surgery can aid substantially in moving towards a quantitative rather than qualitative discussion of perioperative risk.

3.2. *Age*

Functional decline across organ systems, cognitive alterations, and dysregulation of immune responses have all been observed with aging [34]. Therefore, much consideration has been given to the interaction of age with perioperative RC risk. However, the degree to which age-related physiologic alterations impact perioperative RC outcomes remains poorly defined.

There is conflicting evidence regarding an association between age and perioperative outcomes, with several series reporting adverse perioperative outcomes in older patients and other series demonstrating no significant association between age and higher perioperative risk. For example, Schiffmann and colleagues [7] recorded 90-d mortality of 6.4% among patients aged 65–69 yr, compared to 14.8% among patients aged >80 yr, with chronologic age remaining independently associated with the risk of 90-d mortality on multivariable analysis. Furthermore, Nayak et al. [10] observed longer hospital stay, a need for rehabilitation, early mortality, and readmission among older patients. However, Clark and colleagues [35] observed no differences in the rates of early or late complications or operative mortality between decades of age, leading the authors to conclude that chronologic age alone should not necessarily be considered an absolute contraindication for RC. A recent systematic review concluded that although perioperative mortality was higher and overall survival and CSS were lower for greater patient age at RC, a proportion of elderly patients with bladder cancer nevertheless benefit

Table 1 – Comparison of the performance of comorbidity indices and perioperative and oncologic outcomes following radical cystectomy

Study	Patients (n)	MJCs	90-d mortality	Recurrence	Cancer mortality	ACM	NCM
Malavaud 2001 [96]	161	ASA *					
Takada 2012 [97]	928	ASA ^{NS}					
Roghmann 2014 [98]	535	ASA * CCI *					
Garg 2013 [61]	1097	CCI *					
Bostrom 2009 [21]	258	ASA *	ASA ^{NS}				
Fairey 2008 [99]	314		ACE-27 *				
Djaladat 2014 [100]	1964		ASA *	ASA ^{NS}		ASA *	
Schiffmann 2014 [7]	5207		CCI *				
Boorjian 2013 [6]	891		EI * ASA * ECOG * CCI ^{NS}			EI * ASA * ECOG * CCI *	
Mayr 2012 [101]	555		ECOG * ASA * CCI * ACE-27 *		ECOG ^{NS} ASA ^{NS} CCI ^{NS} ACE-2 ^{NS}		ECOG ^{NS} ASA * CCI ^{NS} ACE-2 ^{NS}
Novotny 2016 [26]	1015		ASA * CCI *				
Evers 2013 [102]	234			KPS * ASA ^{NS} CCI ^{NS}	KPS * ASA ^{NS} CCI ^{NS}	KPS * ASA ^{NS} CCI ^{NS}	
Eisenberg 2013 [14]	1776				ECOG * CCI *		
Koppie 2008 [30]	1121				ACCI ^{NS}		ACCI *
Psutka 2014 [48]	205				CCI * ECOG ^{NS} ASA ^{NS}	CCI * ECOG * ASA *	
Mayr 2014 [16]	227				CCI *		
Megwalu 2008 [103]	210					ACE-27 *	
Psutka 2015 [58]	262					ASA * ECOG ^{NS}	
Mayr 2018 [47]	500					ACE-2 ^{NS}	

NS = no statistically significant association with the outcome of interest observed on multivariable analysis; ACE-27 = Adult Comorbidity Evaluation-27; ACM = all-cause mortality; ASA = American Society of Anesthesiology risk score; ACCI = age-adjusted Charlson comorbidity index; EI = Elixhauser index; ECOG = Eastern Cooperative Oncology Group performance status; KPS = Karnofsky performance scale; MJCs = major complications; NCM = non-cancer mortality.

* Statistically significant association with the outcome of interest observed on multivariable analysis.

from curative treatment, underscoring the need for more specific geriatric assessments [36]. In this context, a population-based study from the Netherlands demonstrated that RC utilization was associated with a lower risk of ACM (hazard ratio [HR] 0.4, 95% confidence interval [CI] 0.4–0.5) after adjusting for age, leading the authors to question whether RC may be underutilized among the elderly [37].

3.3. *Body composition and nutrition*

Unintentional weight loss is commonly observed among patients with advanced bladder cancer. It is also a key component of cancer cachexia, a stereotypic syndrome observed across malignancies that is characterized by anorexia, skeletal muscle loss, and variable loss of adipose mass, which has been associated with greater disability and symptom burden, lower tolerance for anticancer treatments, and lower patient-reported quality of life [38]. Of these, sarcopenia is a severe deficiency of lean muscle mass associated with declines in both strength and physical performance [39]. Among cancer patients, loss of lean muscle occurs in an accelerated fashion beyond what would be expected for a patient's age, and has been associated with inferior perioperative and oncologic outcomes across malignancies [40,41].

Lean muscle deficiency can be evaluated using various assessments. The gold standard is the dual-energy X-ray absorptiometry scan [42]. However, muscle mass can also be quantified using measurements of lean muscle cross-sectional areas on standard axial computed tomography (CT) scans [43]. Various metrics have been described for quantifying lean muscularity from axial CT scans. To date, the skeletal muscle index (SMI; total lumbar muscle area at mid-L3 divided by height squared, expressed as cm^2/m^2), which estimates whole-body skeletal muscle mass, is the most strongly validated [44].

Sarcopenia has been reported for 38–69% of patients undergoing RC [44–47] and is independently associated with up to a twofold higher risk of CSM and ACM [45,46,48,49]. Low SMI has also been associated with a higher risk of complications following RC, with the highest risk of severe complications observed among patients in the lowest SMI quartile and highest body mass index (BMI) quartile [50]. In a European cohort of 327 patients,

Table 2 – Association between precise metrics of body composition, including sarcopenia and adiposity, and outcomes following radical cystectomy

Study	*n*	Anthropometric parameter	Measurement	Multivariable point estimates for endpoints of interest
Wan 2014 [50]	247	SMI measured at the umbilicus (L4/L5)	SMI (continuous)	Overall complications: OR 0.98, $p = 0.11$ Clavien grade ≥3 complications: OR 0.952, $p = 0.017$
Psutka 2014 [48]	205	SMI measured at L3	M: SMI <55 cm²/m² F: SMI <39 cm²/m²	CSM: HR 2.14, $p = 0.007$ ACM: HR 1.93, $p = 0.004$
Psutka 2015 [58]	262	SMI measured at L3 FMI (obese class I–III) BMI (obese class I–III)	M: SMI <55 cm²/m² F: SMI <39 cm²/m² M: FMI >9 kg/m² F: FMI >13 kg/m² M/F: BMI >30 kg/m²	ACM: 1.71, $p = 0.01$ ACM: 0.85, $p = 0.45$ ACM: 0.79, $p = 0.33$
Hirasawa 2016 [45]	136	SMI measured at L3	M (BMI <25 kg/m²): SMI <43 cm²/m² M (BMI ≥25 kg/m²): SMI <53 cm²/m² F: SMI <41 cm²/m²	CSM: 2.3, $p = 0.015$
Miyake [104]	89	SMI measured at L3	M (BMI <25 kg/m²): SMI <43 cm²/m² M (BMI ≥25 kg/m²): SMI <53 cm²/m² F: SMI <41 cm²/m²	ACM: HR 2.2, $p = 0.03$ CSM: HR NR, $p = 0.014$
Saitoh-Maeda 2017 [105]	78	PMI measured at the umbilicus (L4/L5)	High: ≥400 cm²/m² Low: <400 cm²/m²	Univariate only Length of stay >30 d: M $p = 0.046$, F $p = 0.41$ OS: male $p = 0.023$ Complications: male 82.9% vs 31.8%, $p < 0.001$
Zargar 2017 [106]	60	Change in TPV during NAC	CTS or ≥5% TPV during NAC	Univariate only Pathologic complete response (CTS): OR 0.95, $p = 0.23$ Pathologic partial response (CTS): OR 0.98, $p = 0.81$ 30-d complications (CTS): OR 1.00, $p = 0.89$ 30-d major complication (CTS): OR 1.00, $p = 0.89$ 90-d readmission (CTS): OR 1.03, $p = 0.47$ RFS (Continuous): HR 0.98, $p = 0.55$ CSS (CTS): HR 1.003, $p = 0.95$ OS (CTS): HR 1.01, $p = 0.74$) RFS (≥ 5% TPV loss): OR 1.41, $p = 0.5$ OS(≥5% TPV loss): OR 1.92, $p = 0.22$ CSS (≥5% TPV loss): OR 2.81, $p = 0.13$
Mayr 2018 [46]	328	SMI (cm²/m²)	M (BMI <25 kg/m²): SMI <43 cm²/m² M (BMI ≥25 kg/m²): SMI <53 cm²/m² F: SMI <41 cm²/m²	Clavien 4a–5 complications: OR 2.84, $p = 0.007$ Clavien 3b–5 complications: OR 2.05, $p = 0.009$
Mayr 2018 [47]	500	SMI	M (BMI <25 kg/m²): SMI <43 cm²/m² M (BMI ≥25 kg/m²): SMI <53 cm²/m² F: SMI <41 cm²/m²	ACM: 1.43, p = 0.01

SMI = skeletal muscle index (cross-sectional area of total lumbar muscle mass at the midpoint of L3, L4, or L5 as specified); FMI = fat mass index (fat mass calculated as the cross-sectional adipose areas at the midpoint of L3 divided by height squared; NAC = neoadjuvant chemotherapy; TPV = total psoas volume; PMI = psoas muscle index; CTS = continuous; CSM = cancer-specific mortality; ACM = all-cause mortality; BMI = body mass index; NR = not reported; M = male; F = female; OR = odds ratio; HR = hazard ratio; OS = overall survival; CSS = cancer-specific survival; RFS = recurrence-free survival.

sarcopenia was independently associated with the risks of major postoperative complications and 90-d mortality [46]. Table 2 summarizes the findings from studies evaluating cross-sectional imaging-based measurements of lean muscularity and sarcopenia as a prognostic factor in RC patients.

When evaluating body composition as a risk assessment metric in RC patients, the presence of obesity should also be considered. When obesity has been defined according to the World Health Organization BMI-based thresholds, there has been a lack of consistency among reports on the association of obesity with perioperative morbidity and mortality. Several retrospective series have demonstrated an absence of association between BMI-based assessments of obesity and postoperative morbidity and mortality [44,51–54], while other studies have reported an association between obesity and higher rates of complications, cancer progression, and death [55,56]. Conversely, others have observed that higher BMI was paradoxically associated with a lower risk of disease recurrence and with prolonged survival [57]. The inconsistency in the observations regarding BMI and post-RC outcomes may reflect the relative lack of specificity of BMI in characterizing true body composition. That is, BMI simply measures weight normalized by height, but does not communicate the balance between lean muscle and adipose burden [58]. This concept was illustrated in a single-institution series of 262 patients for whom adiposity was defined according to sex-specific consensus thresholds based on the fat mass index (FMI, kg/m²) estimated from preoperative CT scans [49]. The correlation between obesity strata as defined by BMI and FMI was poor ($\kappa = 0.41$; $p < 0.001$). To further illustrate the lack of specificity of BMI, of patients with a normal BMI (18.5–24.9 kg/m²), only 12% had "normal" muscle and adipose measurements, while 83% were sarcopenic, with severe lean muscle deficiency, and 5% were sarcopenic obese, also meeting the FMI-based criterion for obesity [49]. Conversely, patients with "normal" body composition had BMI values ranging from <18.5 to 39.9 kg/m² [49]. In

Table 3 – Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition clinical characteristics for the diagnosis of malnutrition in a chronically ill patient: a minimum of two of the six characteristics is recommended for a diagnosis of either severe or nonsevere malnutrition [60]

Clinical characteristic	Nonsevere malnutrition	Severe malnutrition
Energy intake Assessed via review of food and nutrition history and estimation of optimum energy needs compared to estimated energy consumed; inadequate intake is reported as a percentage of estimated energy requirements over time	<75% of estimated energy requirement for ≥1 mo	≤50% of estimated energy requirement for ≥1 m
Interpretation of weight loss Must be interpreted in the context of under- or overhydration	5% over 1 mo 7.5% over 3 mo 10% 0ver 6 mo 20% over 1 yr	≥5% over 1 mo ≥7.5% over 3 mo ≥10% over 6 mo ≥20 over 1 yr
Physical findings Malnutrition typically results in changes in the PE; any of the PE findings may be documented as an indicator of malnutrition		
1. Body fat loss: loss of subcutaneous fat (eg, orbital, triceps, fat overlying the ribs)	Mild	Severe
2. Muscle mass loss: wasting of the temples (temporalis muscle), clavicles/ shoulders (pectoralis and deltoids), interosseous muscles, scapula (latissiums dorsi, trapezius, deltoids), thigh (quadriceps), and calf (gastrocnemius)	Mild	Severe
Fluid accumulation Assessment of accumulated fluid on PE (as dependent edema of the extremities, vulva/scrotum, ascites), which may mask weight loss due to generalized fluid retention	Mild	Severe
Reduced grip strength Consult normative standards supplied by the manufacturer of the measurement device	Not applicable	Measurably reduced

PE = physical examination.

that study, FMI was not associated with CSM or overall mortality after adjusting for lean muscle mass, comorbidity, ECOG-PS, and tumor-specific characteristics [49].

One particularly enticing reason to specifically quantify lean muscularity is that sarcopenia represents a modifiable risk factor. It has been demonstrated that programs to recover muscle loss decrease length of stay and payer and hospital costs following surgery [59]. Given the prevalence of sarcopenia among RC patients and the widespread use of cross-sectional imaging in the management of RC both before and after surgery, such measurements may offer the potential for early identification of high-risk patients who could benefit from prehabilitative interventions. One such prehabilitation study among RC patients has recently completed accrual and a report is expected in the near future (NCT01840137).

Malnutrition is increasingly appreciated as a potentially modifiable risk factor among patients being considered for RC. A consensus guideline statement from the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition recommends classifying malnutrition in chronically ill patients when at least two of the following criteria are met: inadequate food intake, weight loss, loss of subcutaneous fat or muscle mass, fluid accumulation, and lower functional status (Table 3) [60]. Prospective studies have documented malnutrition in 14–55% of RC patients [61,62]. Thus, the impact of inadequate nutritional reserves is increasingly appreciated as a modifiable risk factor for RC patients.

Malnutrition is intimately associated with the syndromes of cancer cachexia and sarcopenia [48,63]. Arends and colleagues [64] proposed a schema for describing the progression of malnutrition in cancer patients, starting with anorexia and a resultant decline in food intake that may be secondary to a combination of cancer, treatment-associated changes in appetite, and potential physical limitations that affect food intake (eg, mouth ulcers, dysphagia, bowel obstruction), resulting in precachexia and cachexia. Subsequent expression of proinflammatory cytokines, including IL-1, IL-6, and TNF-α, results in exacerbation of anorexia and acceleration of catabolic processes that combine to reduce nutrient intake and increase metabolic demands. This process ultimately results in sarcopenia, or end-stage malnutrition, signaling depletion of nutritional reserves with consequent severe loss of muscle mass (Fig. 1).

Various criteria have been used to assess malnutrition, most commonly hypoalbuminemia (albumin <3.5–4 g/dl), BMI <18.5 kg/m^2 (underweight), and/or recent weight loss [54]. Multiple studies have documented an association between preoperative hypoalbuminemia and postoperative complications, length of stay, and higher mortality [54,61,65,66].

Importantly, albumin is an acute phase reactant, and declines in the setting of acute inflammation, which in turn is common among patients with advanced malignancies [64]. Moreover, weight-based assessments such as BMI may obscure advanced markers of malnutrition such as loss of lean muscle and cachexia [49,67]. For this reason, it is recommended that nutritional assessments should be performed using validated screening tools such as the NRS 2002 score, which codifies weight change, food intake, and BMI and includes an assessment of disease severity [68]. This tool has been validated for abdominal surgery and has been prospectively assessed in RC patients, with a trend

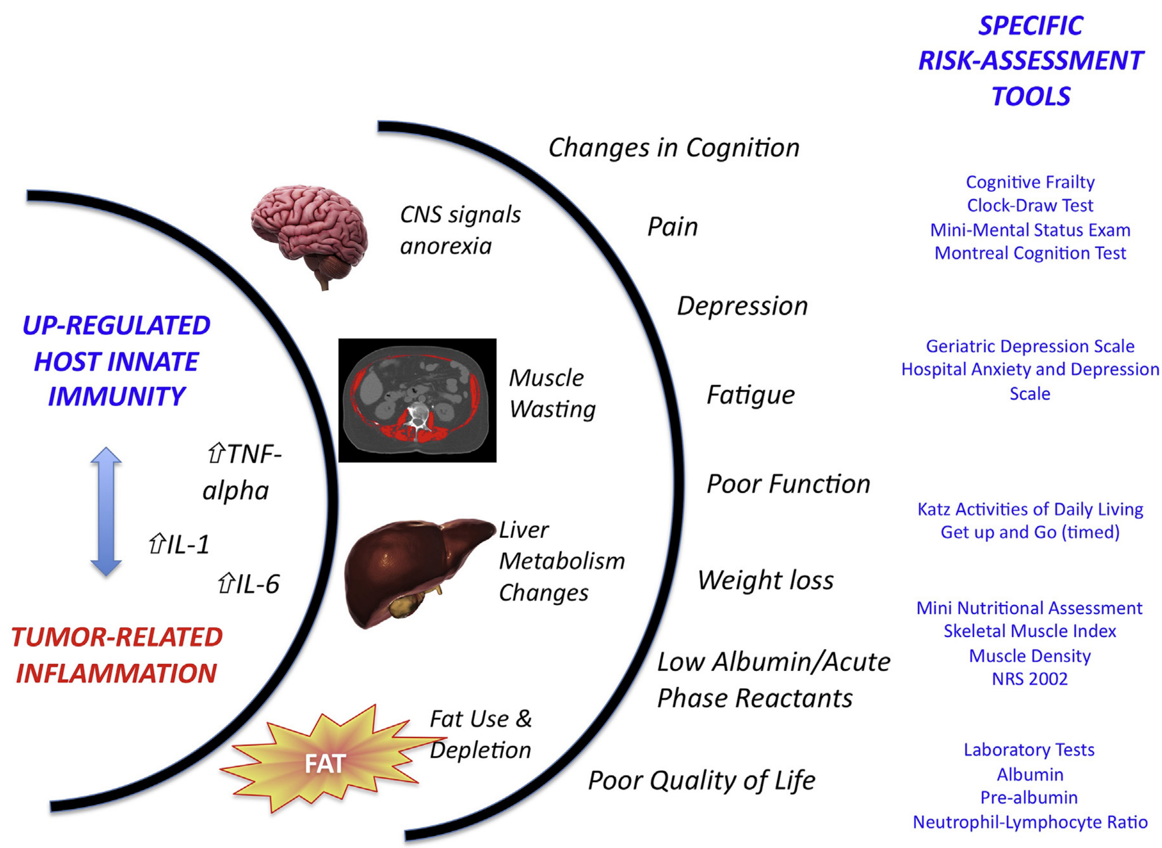

Fig. 1 – Schematic of the progression of cancer-related malnutrition and its impact on the host. Starting with the interaction between tumor-related inflammation and host-related immunity, changes in central nervous system (CNS) signals regulating appetite and/or anorexia, acceleration of lean muscle wasting, metabolic changes, and fat depletion result in a myriad of outcomes that affect patients with localized bladder cancer. Candidate risk assessment instruments to identify the complications of cancer-related malnutrition are listed.

towards higher complication rates for patients with higher NRS scores observed [62].

While national (AUA, EAU) and organizational (National Comprehensive Cancer Network) urologic guidelines have not yet addressed this topic, updated guidelines from the European Society for Clinical Nutrition and Metabolism [64] for the assessment and management of cancer-related malnutrition recommend screening of nutritional status early in the course of treatment, with the goal of early identification of signs and symptoms of anorexia, cachexia, and sarcopenia. In patients with malnutrition, preoperative nutritional interventions such as immunonutrition supplements are associated with lower rates of postoperative complications and may mitigate some of the postoperative inflammatory response following RC [69,70]. Future studies are needed to further understand the optimal nutritional interventions in the perioperative period for RC patients and to characterize the impacts of intensive nutritional interventions on post-RC outcomes.

3.4. Multidimensional assessments of physiologic age

3.4.1. Frailty

Frailty is a state of age-related physiologic vulnerability that may result in lower ability of a patient to withstand stress [71]. A recent international consensus statement highlighted the prognostic potential of this construct, specifying that frailty is "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases and individual's vulnerability for developing increased dependency and/or death" [72]. In contrast to the conventional comorbidity indices previously discussed, frailty is a multidimensional construct that comprises various aspects of vulnerability to stressors, which importantly can be measured objectively using standardized instruments. With growing appreciation of how frailty can influence health care outcomes [73], there is interest in understanding how frailty assessments may be of benefit in pre-RC perioperative risk stratification [74].

While there is increasing awareness of the concept of frailty, it has been demonstrated that a surgeon's gestalt impressions of frailty and patients' perception of their own frailty and ability to withstand the stress of surgery are discrepant from objective metrics of physiologic reserve [75]. Traditional assessments of frailty such as the Fried frailty phenotype include at least three of the following: unintentional weight loss, self-reported exhaustion and depression, and functional measurements of weakness assessed in terms of grip strength, walking speed, and physical activity over extended periods of time [71]. The criteria for commonly used frailty metrics are presented in

Table 4 – Frailty assessments

Frailty metric	Assessment tools and criteria
Fried frailty phenotype [71]	1. “Shrinking”:
	a. Unintentional weight loss (>10 lb unintentional weight loss over 1 yr)
	b. Sarcopenia: loss of muscle mass
	2. Weakness: grip strength in the lowest 20% according to gender and body mass index
	3. Poor endurance; exhaustion:
	a. Slowness: walking time for 15 feet: slowest 20% by gender and height
	b. Low activity: lowest 20% kcal/wk by gender (males <383, females <270 kcal/wk
	Presence of frailty phenotype: ≥3 criteria present
	Intermediate/pre-frail: 1 or 2 criteria present
Canadian Study of Health and Aging frailty index [107]	Assessment of 70 variables measuring the presence and severity of current disease, ability for ADL, and physical and neurological signs from clinical examination of mobility, function, and self-rated health
	Index = total number of deficits identified/total number of deficits measured
FRAIL scale [108]	Five items reflecting performance, self-reports, and common comorbidities:
	1. Do you feel worn out/tired?
	2. Ability to climb one flight of stairs
	3. Ability to walk 100 m
	4. Self report of >5% weight loss
	5. More than 5 conditions among dementia, heart disease, depression, arthritis, asthma, bronchitis/emphysema, diabetes, hypertension, osteoporosis, and stroke
Clinical frailty scale [109]	1. Very fit: individuals who are robust, active, energetic, motivated, and fit; those who exercise regularly and are in the most fit group for their age
	2. Well: without active disease, but less fit than individuals in category 1
	3. Well, with treated comorbid disease: disease symptoms are well controlled compared to those in category 4
	4. Apparently vulnerable: although not frankly dependent, these individuals commonly complain of being “slowed up” or have disease symptoms
	5. Mildly frail: with limited dependence on others for instrumental ADL
	6. Moderately frail: help is needed with both instrumental and non-instrumental ADL
	7. Severely frail: completely dependent on others for ADL, or terminally ill
Modified frailty index [76]	1. Functional health status before surgery (partially/totally dependent)
	2. Diabetes mellitus (type II)
	3. Chronic obstructive pulmonary disease
	4. Congestive heart failure
	5. History of myocardial infarction within 6 mo
	6. Prior cardiac surgery, percutaneous coronary intervention, or angina within 1 mo
	7. Hypertension
	8. Impaired sensorium
	9. History of transient ischemic attack
	10. History of cerebrovascular accident
	11. Peripheral vascular disease requiring surgery or active claudication present
	Index = number of factors present/11
	Robust: 0–0.09; pre-frail: 0.09–0.18; frail: ≥0.27
Simplified frailty index [79]	1. Diabetes
	2. Functional status
	3. Chronic obstructive pulmonary disease
	4. Congestive heart failure
	5. Hypertension
	Scored as 1, 2, or ≥3 risk factors

ADL = activities of daily living.

Table 4. However, the use of such assessments is onerous in daily clinical practice and they are therefore of limited practical utility.

In this context, abbreviated frailty indices have been constructed and validated, including the 11-item modified frailty index (mFI) [76]. Chappidi and colleagues [77] assessed 2679 RC patients from the National Surgical Quality Improvement Program (NSQIP) and observed that the presence of two or more mFI risk factors was independently associated with an higher risk of major 30-d complications, while Pearl et al. [78] found that frailty was independently associated with discharge to a facility other than the patient’s home. Moreover, a simplified frailty index), derived from an RC population within NSQIP, had similar predictive ability to the mFI and outperformed the ASA score with respect to predicting major complications and discharge destination [79].

The converse of frailty is physical fitness and physiologic reserve. One active focus of research in this area is preoperative risk stratification using cardiopulmonary exercise testing to measure a patient’s anabolic threshold. It has been prospectively demonstrated that low cardiopulmonary reserve is associated with a higher risk of postoperative complications and longer hospital stay after RC [80].

In addition to the physical domain of frailty, cognitive frailty is also recognized as a risk factor for poor health-related outcomes. Assessments of cognition have recently been incorporated into the definition of frailty, and in 2013 an international consensus group proposed that *cognitive frailty* should be defined as "a heterogeneous clinical manifestation characterized by both physical frailty and cognitive impairment in the absence of concurrent Alzheimer's disease or dementia" [81]. Poor cognitive function has significant implications for RC patients in terms of their ability to provide informed consent, to adhere to treatment plans, and to recognize and report toxicity and complications of therapy and/or surgery.

Makhani et al. [82] assessed physical frailty using the Fried frailty score and cognition using the Emory clock draw test in 330 patients undergoing major surgical interventions, including 25 patients who underwent RC [82]. Interestingly, neither the ASA score nor CCI differed significantly across patients who were classified as robust (51%), or with cognitive impairment only (29.1%), physical frailty only (12.1%), or both physical and cognitive impairment (7.9%). On multivariable analysis, the combination of physical and cognitive frailty was independently associated with fourfold higher risk of ACM (HR 4.23, 95% CI 2.0–8.8). Further research, ideally using prospectively assessed clinical data sets, is needed to characterize how frailty should be best assessed and incorporated into preoperative evaluation of RC patients.

3.4.2. Comprehensive geriatric assessments

One proposed approach for more efficient assessment of the complex interplay between biological and functional age for perioperative risk stratification of fitness for surgery is a comprehensive geriatric assessment (CGA) [83]. CGA is a multidimensional evaluation of health that incorporates assessments of function and ability, disease severity and comorbidity, mental health and cognition, and the support networks and specific needs of a patient, with the goal of identifying potentially modifiable risk factors for which individualized treatment plans can be developed [83]. Specifically, the CGA assesses seven domains: functional status, comorbidity burden, polypharmacy, cognition, psychologic status including anxiety and depression, social support, and nutrition.

CGAs provide improved discrimination in risk assessment compared to traditional tools such as ECOG-PS. For example, although approximately 80% of elderly patients with cancer have an ECOG-PS of 0–1 (fully active with no restrictions or mild restrictions for strenuous activities), more than half of these patients require assistance with their activities of daily living [84], which has substantial implications for a patient undergoing consideration for a major surgical procedure such as RC. In fact, a meta-analysis demonstrated that among elderly hospitalized patients with a normal ECOG-PS, CGA identified a significant abnormality in 61%; and among those with a normal ASA, CGA was abnormal in 65% [85].

In surgical series, CGA scores have been associated with adverse outcomes including postoperative complications, delirium, prolonged hospital stay, readmission, and discharge to places other than home [86]. The ability of CGAs to influence RC treatment decisions remains to be described, and therefore represents an important area for future study.

3.5. *Other factors to consider in pre-RC risk assessment and future directions*

Beyond factors such as frailty, comorbidity, and functional age, there are individual patient factors that may contribute to perioperative risk and long-term outcomes that warrant consideration. These include a critical assessment of the patient's priorities with respect to the outcome measures most meaningful to that patient and his or her family, such as ability to return home, or return to work or specific activities. Other factors such as surgical history [87], prior radiation exposure [88], substance use (eg, tobacco, alcohol, and recreational drugs) [89], and health literacy [90,91] may also influence perioperative outcomes and merit consideration when assessing a patient's fitness for RC, and in counseling regarding anticipated short- and long-term outcomes.

The integration of multidimensional assessments into clinical urologic oncology practice requires the development of multidisciplinary partnerships between urologists, geriatricians, and nutritionists who have expertise in administering these assessments, as well as streamlining the process of collecting the data and integrating it into electronic health records for operationalization of these metrics into busy urologic practice. Other challenges to be addressed include the operationalization of morphometrics in collaboration with radiologists and greater incorporation of social workers and case workers to assist clinicians in better assessing home support.

Finally, with increasing use of neoadjuvant chemotherapy and anticipated data regarding neoadjuvant immunotherapy, there is a defined interval for patients undergoing preparation for RC in which prehabilitative interventions may be undertaken to optimize physical function, nutrition, and frailty. Ongoing trials assessing the impact of preoperative interventions targeting nutrition, physical fitness, and function such as bladder cancer "boot camps" and interventions guided by automated wearable fitness trackers are anticipated, and reports are expected in the near future [92,93].

4. Conclusions

Preoperative risk assessment for patients being considered for RC is complex. Although prognostic tumor features in bladder cancer have been well defined, we have yet to define the optimal means by which a surgeon may "stage the host". Conventional assessments of chronologic age, comorbidity burden, BMI, nutrition, and performance status alone may not fully characterize an individual patient's functional age and risk profile. Standardized multidimensional risk stratification tools that allow more refined overall risk assessments are available, including CGAs, formal nutritional evaluations, frailty scores, and precise measurements of muscle mass. In addition to offering individualized global risk assessments, these tools may identify potentially modifiable risks to guide interventions such as prehabilitation and other modes of surgical optimization, or, among patients with substantial risk profiles, to identify more appropriate candidates for alternative bladder-sparing approaches.

To date, no studies have prospectively evaluated CGA among bladder cancer patients. However, the 2017 EAU guidelines for MIBC, the National Comprehensive Cancer Network guidelines, and the International Society for Geriatric Oncology all advocate for CGA use for patients aged >70 yr and consideration of CGA use for younger patients with age-related health concerns [2,94,95]. Prospective studies using these more specific and comprehensive assessments in clinical practice are needed to define their utility in predicting the risks of perioperative and long-term outcomes.

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Acquisition of data: Psutka, Barocas, Catto, Gore, Lee, Master, Morgan, Necchi, Rouprêt, Boorjian.
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Appendix A. Supplementary data

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