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Assessments of frailty in bladder cancer

Dominic C. Grimberg[a], Ankeet Shah[a], Jeroen Molinger[b], John Whittle[b], Rajan T. Gupta[c], Paul E. Wischmeyer[b], Shelley R. McDonald[d], Brant A. Inman[a,*]

[a] *Division of Urology*
[b] *Department of Anesthesiology*
[c] *Department of Radiology*
[d] *Division of Geriatric Medicine, Duke University Medical Center, Durham, NC*

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Abstract

Background and Aims: The incidence of frailty is increasing as the population ages, which has important clinical implications given the associations between frailty and poor outcomes in the bladder cancer population. Due to a multi-organ system decline and decreased physiologic reserve, frail patients are vulnerable to stressors of disease and have poorer mortality and morbidity rates than their nonfrail peers. The association between frailty and poor outcomes has been documented across multiple populations, including radical cystectomy, creating a need for frailty assessments to be used preoperatively for risk stratification. We aim to provide a review of the common frailty assessments and their relevance to radical cystectomy patients.

Findings: A variety of assessments for frailty exist, from short screening items to comprehensive geriatric assessments. The syndrome spans multiple organ systems, as do the potential diagnostic instruments. Some instruments are less practical for use in clinical practice by urologists, such as the Canadian Study of Health and Aging Frailty Index and Comprehensive Geriatric Assessment. The tool most studied in radical cystectomy is the modified Frailty Index, associated with high grade complications and 30-days mortality. Frailty often coexists with malnutrition and sarcopenia, stressing the importance of screening for and addressing these syndromes to improve patient's perioperative outcomes.

Conclusions: There is no universally agreed upon frailty assessment, but the most studied in radical cystectomy is the modified Frailty Index, providing valuable data with which to counsel patients preoperatively. Alterations in immune phenotypes provide potential future diagnostic biomarkers for frailty.

Keywords: Frailty; Bladder cancer; Physical activity; Diet; Lifestyle

1. Introduction

Frailty is the phenotype of declining physiologic function and loss of functional reserve across organ systems, leading to vulnerability against disease and death [1−4]. The number of elderly patients undergoing surgical procedures is increasing at an even faster rate than the general population's aging due to advances in anesthesia and perioperative medicine, leading to increasing prevalence of frailty in surgical patients [5]. Frailty has been reported in 7 to 10% of community dwelling adults older than 65 [1] and 21.8% of urologic patients above 70 [6]. Across multiple methods of defining frailty, it is linked to increased ICU stay, hospitalization, readmission, and mortality rates

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*Corresponding author: Tel: 919-684-1322, fax: 919-668-7093
E-mail address: brant.inman@duke.edu (B.A. Inman).

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Table 1
Comparison of commonly used frailty functional assessment tools in urologic oncology

Tool	Contents	Scoring
Fried Frailty Criteria (FFC)	Fried Phenotype Components: -weak grip strength -slow gait -decreased activity level -unintentional weight loss -feelings of exhaustion	0−1: Not frail 2−3: Intermediately frail 4−5: Frail
Clinical frailty scale (CFS)	7 point scale from "1- Very Fit" to "7- Severely Frail" ascertained by clinician judgement	5: Mildly frail 6: Moderately frail 7: Severely frail
Canadian Study of Health and Aging Frailty Index (CSHA-FI)	70 Deficits (Appendix 1) including symptoms, signs, disabilities, and comorbidities spanning physical, functional, social, and cognitive domains	Deficits totaled and represented as a fraction of the 70-total deficits (i.e. 0-1.0) with higher scores indicating more frail patients
Modified Frialty Index (mFI)	11 Deficits: -Nonindependent functional status -History of diabetes mellitus -History of COPD -History of congestive heart failure -History of myocardial infarction -History of percutaneous coronary intervention, cardiac surgery, or anging -Hypertension requiring medication -Peripheral vascular disease or rest pain -Impaired sensorium -Transient ischemic attack or cerebrovascular accident without residual deficit -Cerebrovascular accident with residual deficit	≥3 deficits: Frail
Center for Epidemiological Studies Depression (CES-D) scale	Twenty question list of depressive symptoms to which patients respond 0 (rarely or none), 1 (some or a little of the time), 2 (moderate amount of time), or 3 (most of the time) and points totaled.	≥16 points: Depression

[4−6]. Specific to radical cystectomy, frailty rates are associated with higher complications and mortality [7−8]. Due to the increasing likelihood of frailty pre- and post-operatively; there is a need for accurate identification of frailty to inform risk assessment and shared decision making [9,10]. Unfortunately, frailty screening tools are rarely used in urologic practice, in part due to the lack of consensus on an optimal tool for radical cystectomy patients.

2. Functional assessment of frailty

There is no consensus on how to define frailty clinically and despite an abundance of tools, scales, and instruments there is no standard method for screening frailty in routine clinical practice [11]. Furthermore, frailty is a dynamic condition; patents may move between robust, prefrail and frail states throughout their clinical course. Approaches are varied and range from prospective assessments involving physical assessment alongside clinical history, to techniques relying entirely on electronic health record diagnosis codes [12−21].

The most conceptually simple measure is the Clinical Frailty Scale (CFS), developed using data from the Canadian Study of Health (CSHA) (Table 1) [22,23]. This tool considers a patient's cognition, mobility, function, and comorbidities to assign patients based on physician judgement into 1 of 7 categories ranging from robust health (1) to complete functional dependence on others (7) [23]. Subsequent validation showed an incrementally increasing risk of 5-year mortality and entry into an institutional facility with increasing CFS [23].

Beyond clinician judgment (demonstrated to be inaccurate and unreliable) [16], 2 more complex conceptual models exist to describe frailty: the frailty phenotype (Fried) [4] and frailty index (Rockwood) [23]. The Fried phenotype defines frailty by the following criteria − impaired grip strength, gait speed, physical activity, unintentional weight loss and self-reported exhaustion. The second conceptual model, an accumulation of deficits model, reflects the number of deficits an individual accrues across a number of domains. An assessment using the deficit model, the CSHA Frailty Index (CSHA-FI), consists of 70 deficits including symptoms, signs, disabilities, and diseases to cover physical, functional, social and cognitive domains as well as incorporating comorbidities (Table 1) [23]. The multi-system nature of frailty is exemplified in another frailty

assessment, that for cognitive frailty, which combines physical frailty or prefrailty as defined by common criteria with cognitive decline measured via Mini-mental status exam or Montreal Cognitive Assessment [24−27].

Another accumulation of deficits instrument used in the surgical context is the modified Frailty Index (mFI), Table 1) [20,28]. An abbreviation of the 70 item CSHA-FI, this was developed using 11 items that are widely available from the National Surgical Quality Improvement (NSQIP) database [29]. Of these 11 items, 10 are comorbid conditions and one relates to patient's functional status. An mFI score of 3 above signifies frailty and is better than ASA score at predicting postoperative complications [30]. The tool has been validated for use in urologic oncology surgeries using NSQIP data with similar predictive ability for 30-days mortality and grade IV complications to ASA score, CCI, and CSHA-FI, however sensitivity and specificity are higher for prostatectomy and nephroureterectomy than for cystectomy [18].

In the context of frailty in urologic oncology, most studies have been retrospective database reviews utilizing mFI to categorize frailty. One such examination of 2679 NSQIP patients who underwent radical cystectomy demonstrated an increasing risk of Clavien IV or V complications with an mFI score of 2 or 3 (odds ratio [OR] 1.84 [1.28−2.64]) and 2.58 [1.47−4.55]) [8]. Another retrospective NSQIP analysis of common urologic surgeries demonstrated increases in 30-days complications (total, major, and minor) with increasing mFI (OR 1.28 [1.21−1.36] for mFI=1, 1.74 [1.64−1.85] for mFI ≥2). However after limiting to radical cystectomy frailty was no longer associated with increased complication risk [31]. A prospective study of 134 patients undergoing radical cystectomy showed patients with at least 2 elements of the Fried Frailty Criteria (FFC) had a higher 30 days grade IIIa-V complication rate. Objective frailty assessments such as FFC and gait speed were more predictive than subjective instruments (ECOG, CES-D, self-reported symptoms) [32].

Unfortunately, agreement between frailty assessment tools is poor especially in the radical cystectomy population. An analysis of 1516 radical cystectomy patients from the NSQIP database showed that mFI, CCI, and ASA score all had poor discriminative ability for severe adverse events (AUC < 0.52 for all) [33]. Soma et al. developed a 10-item abbreviated comprehensive geriatric assessment (CGA) tool dubbed the Frailty Discriminant Score (FDS), which was validated in a cohort of 605 patients with urologic cancers and over 2,000 noncancer controls to correspond with FFC and predict overall survival. However, their subsequent prospective study showed only fair agreement in defining frailty between FDS and FFC, with FDS missing 26% of those categorized as frail by both FFC and the G8 screening questionnaire [34].

Another instrument, accepted as the criterion standard for frailty assessment, is the CGA [35]. However, in addition to being time consuming, most surgeons have limited training in CGA implementation and interpretation and therefore rely on multidisciplinary care with geriatricians, which may not be feasible in all settings [28].

3. Comprehensive geriatric assessments

CGA is a process for developing the plan of care for frail older adults with complex health problems and needs using interprofessional teams to address not only pertinent medical conditions, but their psychological status and functional abilities within social and environmental contexts [36]. Older adults often have subtle and sometimes difficult to elicit patient factors that are best identified with targeted assessments obtained from specialized health providers in geriatrics, geriatric resource nursing, social work, nutrition, speech therapy, physical and occupational therapy, and pharmacy. Fully understanding the circumstances in an older adult's life when a significant health stressor arises such as surgery, intensive medical therapy, or hospitalization allows for not only better anticipation of complications and appropriate planning for risk mitigation but also optimization of treatable conditions.

Two Cochrane systematic reviews of older adults receiving CGA as part of in-patient hospital care show that patients are more likely to return to their home following hospital discharge for up to 12 months afterwards. This was first examined in 2011 with 22 trials evaluating 10,315 participants (OR 1.16, 95% confidence interval [CI] 1.05 −1.28, $P = 0.003$) [37] and in 2017, with in 16 trials of 6799 participants (Risk Ratio 1.06, 95% CI 1.01−1.10) [38]. The evidence does not support a mortality benefit, reduced dependency or cognitive benefit for medical patient receiving CGA. It should be noted that the choice of outcome measure, discharge disposition, is also impacted by physician preference and health system (private vs. national).

There is less evidence for the benefits of CGA in surgery, but systematic review shows patients requiring hip surgery have reduced mortality and are more likely to return directly to home upon discharge [39]. Partridge et al. performed an RCT in patients pursuing elective vascular surgery, and those receiving CGA with preoperative visits and surgical staff following the documented individualized care plans during hospitalization had a 2-days reduction in length of stay (LOS) and reduced postoperative medical complications [40]. Another recent study in older adults undergoing elective abdominal surgeries with preoperative CGA followed by geriatric hospital comanagement also had a 2-days reduction in LOS and fewer postoperative complications [41]. The effectiveness of delivering CGA as an interprofessional team compared with the delivery on specialty-based wards is uncertain [38], although a quality improvement project for elective and emergency urology patients aged ≥65 years, supports the conclusion that even components of a CGA reduce LOS and reduce postoperative complications [42]. The Proactive care of Older People

undergoing Surgery (POPS)-Urology is a structured geriatrics liaison service where weekly interdisciplinary team meetings were used to identify high-risk patients that were then seen by geriatricians. While the benefit from a CGA to provide patient-centered multidimensional care for frail complex patients is becoming clear, the metrics to identify those who will benefit the greatest is not well delineated and needs further exploration.

4. Sarcopenia and imaging techinques in frailty

Physical deconditioning, including reduced aerobic fitness, is a significant driver of adverse outcomes after urologic surgery and should form part of the assessment process [43]. Cardiopulmonary exercise testing is the gold standard assessment for aerobic fitness, highly predictive of outcome after urological surgery and may be used not only to aid in risk assessment and diagnosis of comorbidity but in prescription and evaluation of physical prehabilitation [44].

Impaired aerobic fitness overlaps with another key contributor to functional decline secondary to frailty: sarcopenia. Sarcopenia is a progressive and generalized skeletal muscle disorder involving accelerated loss of muscle mass and function. This muscle loss is associated with adverse outcomes including fall-risk, decline in functional status, and increased mortality [45]. Identification of sarcopenia can be challenging since frailty can manifest differently in within individuals, the first step therefore is creating awareness and the need to assess.

The occurrence of sarcopenia in frailty is a crucial discriminatory phenotype. The presence of sarcopenia in urology patients is associated with worse outcomes after surgery, chemotherapy and hormone therapy [46–48]. Sarcopenia is highly prevalent in the urology population, present in up to 67% of radical cystectomy patients and is exacerbated by various lifestyle and clinical factors, including decreased physical activity, altered hormonal milieu, decreased caloric intake, inflammation and altered metabolism secondary to common conditions. Bladder cancer patients with sarcopenia have a higher incidence of chemotherapy-related toxicity, poorer surgical outcomes, and reduced overall survival. Recent studies have attempted to determine the extent to which nonmodifiable risk factors (e.g., age, gender, and race), modifiable lifestyle risk factors (e.g., diet and physical activity), or cancer-related factors (e.g., tumor stage) are related to smooth muscle mass and sarcopenia in BC. Functional assessments such as muscle strength testing are predictive, but focus is being placed on the use of staging and surveillance radiographic studies to quantify muscle volume, quality and other measures of body composition [49].

Muscle volume loss alone, however, does not explain the relationship between sarcopenia and adverse perioperative outcome. Denervation and mitochondrial dysfunction are implicated in skeletal muscle atrophy due to aging and may play a role in the frailty syndrome and provide an alternative explanation for the relationship between reduced aerobic exercise capacity and adverse surgical outcomes [9,12,50]. Denervation, which plays a modulating role in skeletal muscle mitochondrial function in frail women, could be a target for therapeutic strategies such as exercise prehabilitation [51]. The association of prefrailty status in the elderly with mitochondrial impairment in skeletal muscle is strong and provides a rationale for employing strategies that improve mitochondrial function and aerobic capacity, with the goal to reverse or delay the prefrailty phenotype [12].

Currently, sarcopenia largely remains undiagnosed as it is often difficult to differentiate from overall weight loss, especially in obese patients [52]. Morphometric assessments using imaging techniques have garnered increasing interest. Computerized tomography lean body mass analysis has been studied to assess preoperative ‘metabolic reserve’ and ‘fitness for surgery’. This innovative technique may effectively identify patients at higher risk for malnutrition and poor surgical outcomes in a noninvasive and quantifiable way [49,53].

Given observational evidence for the impact of sarcopenia in perioperative outcomes, there is a need for prospective trials to investigate this association. We need objective methods to preoperatively quantify sarcopenia and define standard risk cutoffs for sarcopenia-based measures. Simple screening tools, including imaging techniques, can easily be deployed and positive screens should result in more comprehensive multidisciplinary assessment, prehabilitation and perioperative care.

5. Nutritional assessments: Identification of malnourished bladder cancer patients

Unrecognized malnutrition may among the most pressing “silent epidemic’s” facing cancer patients today. Although it is well known that >30% of hospitalized patients is malnourished at admission [54], older data estimates only 3% are recognized and diagnosed, and even fewer are treated [55]. This is tragic as mortality is 5 times greater for patients diagnosed with malnutrition versus well-nourished patients [55]. Further, patients with preexisting malnutrition and/or weight loss have a 2- to 3-fold increased risk of developing C. difficile enterocolitis, surgical-site infection, or postoperative pneumonia and a >5-fold higher risk of catheter-associated urinary tract infection [56]. More troubling, data in hospitalized patients diagnosed with malnutrition reveals <14% of these malnutrition-related stays included meaningful nutrition intervention [55]. This suggests there is a large proportion of patients whose malnutrition remains undiagnosed and untreated during cancer and other care. Thus, malnutrition is perhaps the least often identified patient risk factor and is among the most treatable to improve outcomes.

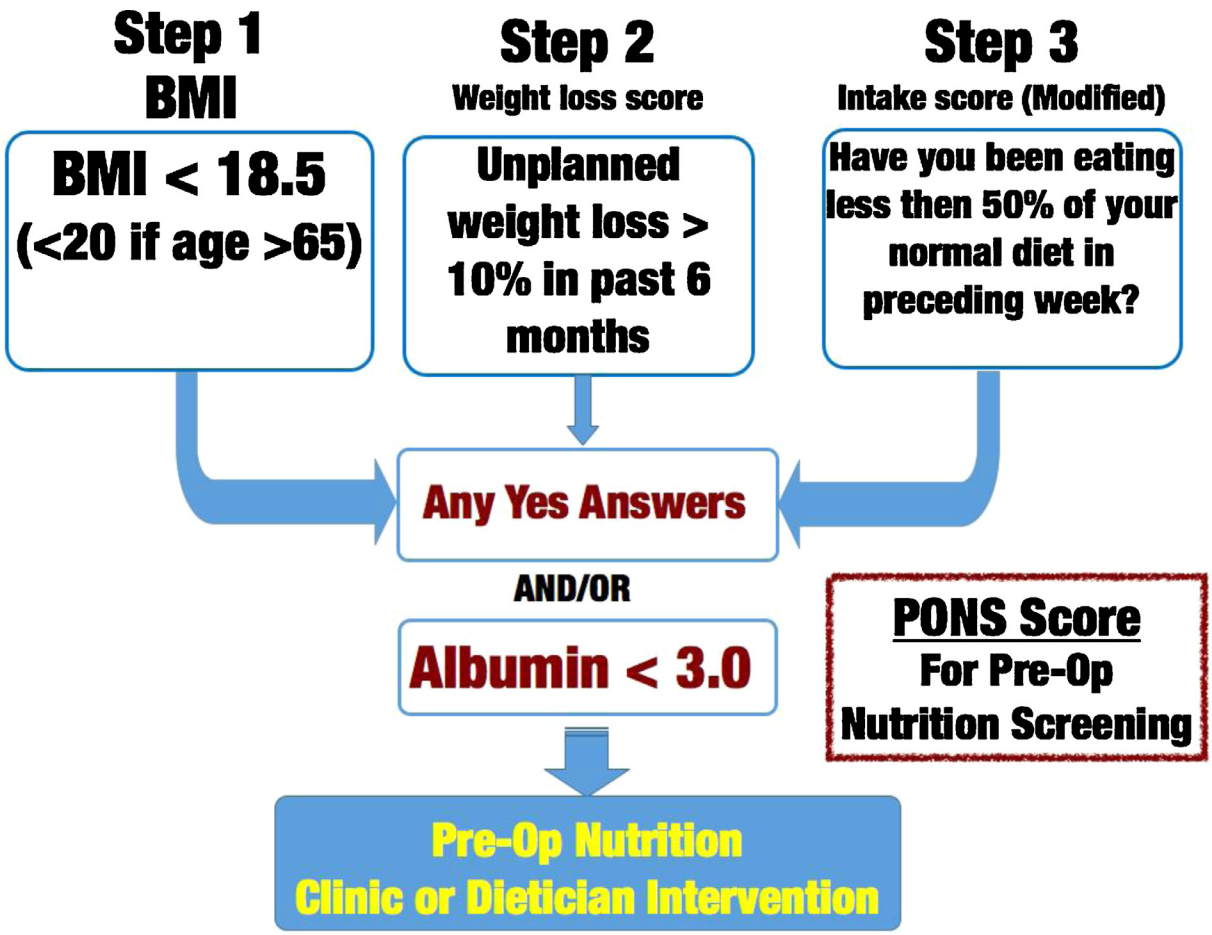

Fig. 1. Perioperative Nutrition Screening (PONS) algorithm for quick and efficient preoperative malnutritional risk identification.

Screening for malnutrition in bladder cancer is essential at diagnosis to identify patients at risk for malnutrition who may benefit from nutritional intervention before, during, and after cancer care. Commonly utilized tools include the Malnutrition Universal Screening Tool (MUST), widely used screening tool to identify adults at risk of malnutrition [57]. Recent evidence indicates MUST Score may not be ideal in oncology patients as it does not adequately address cancer-specific risks such as nutritional intake limiting symptoms including taste/smell alterations, nausea, and swallowing problems. Nutrition screening tools performing better in outpatient oncology patients include The Malnutrition Screening Tool [58], which has good sensitivity in chemotherapy and radiation therapy patients. In the inpatient oncology setting, the Royal Marsden nutrition screening tool [59] is quite sensitive and performs well to identify patients at malnutrition risk. Another alternative is the Subjective Global Assessment questionnaire (PG-SGA) [60], which shows high sensitivity and specificity in detecting malnutrition risk in oncology. Irrespective of which tool is used, it is vital the same tool is used in all settings for a particular patient, and that nutrition screening occurs as early as possible to determine nutrition risk and guide care.

No universally accepted screening tool for preoperative malnutrition risk has been available until publication of the Perioperative Nutrition Screen (PONS) for preoperative malnutrition assessment (Fig. 1) [61]. PONS was developed as a modified version of the MUST score and identifies nutrition risk based on a patient's preoperative body mass index, patient-reported recent decrease in dietary intake, albumin level, and recent weight loss [61]. PONS allows quick and efficient malnutritional risk identification and should be routinely performed on all patients during preoperative assessment before major cancer surgery. Delaying major oncologic surgery should be considered, when possible, in patients with any positive answer to a PONS question, indicating high malnutrition risk. This allows for nutrition optimization as described in existing guidelines and other recent publications [61,62]. Although the optimal time for preoperative nutrition optimization is unclear, it appears a minimum of 7 to 10 days can improve outcomes. Risk of cancer progression from this short delay should be weighed against the significant risk of operating on a malnourished patient.

6. Inflammatory biomarkers/markers of immune activation

Inflammation is widely considered to be a cause of frailty and the increased susceptibility to chronic morbidity, disability, and death that often coexists with frailty [2,63,64]. Immune dysfunction from lifelong chronic inflammatory state is a predisposing factor for many age-related chronic illnesses seen in frailty including atherosclerosis, diabetes, dementia, cancers, Parkinson's, and osteoporosis [1,2,64,65]. Multiple cross-sectional studies describe elevated immune and inflammatory biomarkers in patients meeting frailty criteria, who are also at increased risk for perioperative complications [1,2,66]. Inflammaging and immunosenescence are proposed mechanisms behind these clinical findings that are often seen in the bladder cancer population [8].

Inflammaging refers to a pro-inflammatory state that develops in older patients and is associated with increased susceptibility to morbidity and frailty [63]. Due to sustained immune system activation and antigen presentation, there is a decline in the adaptability of the immune system over time. Multiple potential etiologies for the baseline chronic inflammation exist including increased gut permeability, cellular senescence, impaired autophagy, and impaired cellular material elimination processes leading to accumulation of reactive oxygen species and inflammatory cascade activation [65]. Cellular studies have demonstrated an age-dependent reduction in the phagocytic capabilities of neutrophils, macrophages, and NK cells [67]. Due to this dysfunction, not only is there baseline inflammatory activation but the response becomes less effective and inflammation takes longer to resolve after an acute episode [65]. Levels of inflammatory markers have long been proposed as biomarkers of frailty given the association between pro-inflammatory states and frailty. The most studied inflammatory markers are CRP, TNF-α, and Il-6, which have been shown across multiple populations and definitions of frailty to predict frailty [2,65]. A study of 354 lung transplant candidates showed that patients who met Fried's criteria for frailty had higher IL-6, TNF-α, IGF-1, and leptin levels, and had higher rates of death or delisting prior to transplant [68].

Immune senescence is the process by which patients' adaptive immune system loses its ability to recognize new antigens and develop long-term immune memory due to alterations in the production of T lymphocytes [3]. The Swedish OCTO and NONA studies demonstrated the "immune risk" phenotype characterized by inverse CD4:CD8 lymphocyte ratios and poor T cell proliferation was predictive of increased 2-year mortality [65,69,70]. A study of immune profiles in elderly patients undergoing chemotherapy for breast cancer observed increases in CD8 populations over the course of treatment leading to a worsened CD4:CD8 ratio. Pretreatment immune profile, specifically lower levels of myeloid derived suppressor cells, was also associated with unexpected hospitalizations during treatment [71]. Studies of *p16ink4a* expression, which encodes a protein that leads to cell senescence by blocking cyclin-dependent kinase, demonstrated clear relationships between expression and age, with a 10-fold increase between the ages of 20 and 80. Expression also increases abnormally in patients undergoing chemotherapy for malignancy, suggesting a potential role for *p16ink4a* as a biomarker of the accelerated aging process induced by cancer and cancer treatments [72]. As a sum result of these changes, frail patients are less likely to mount an appropriate humoral response to pathogenic stimuli [3].

Overall, the age-related effects on their innate and adaptive immune systems leave patients vulnerable and unable to mount appropriate responses to new stresses such as infection and surgery, or respond to treatments dependent on an intact immune system. Analyses of nivolumab use in lung cancer revealed that the survival benefit over chemotherapy seen in the overall population was diminished or lost in patients older than 75, likely in part due to their aging immune systems [73].

7. Conclusions

In summary, frailty is a multidimensional state of loss of physiologic reserves that result in a decreased ability to withstand physiological stressors. Preoperative interventions (including physical and nutritional prehabilitation) aimed at improving outcomes after urological cancer surgery, are especially important for frail patients. Measurement tools and diagnostic biomarkers need therefore not only to be sensitive and specific at detecting frailty, but also time-efficient, and employ widely available or easily obtained data in order to lend themselves to routine screening application in the perioperative setting. The 11-item mFI can be easily used in the clinic, and is the most studied in the radical cystectomy population providing valuable data to inform risk assessment and preoperative counseling. Unfortunately, agreement between instruments is poor as their components vary. Those with objective measures, such as mFI, are likely more accurate but further studies are required to determine the ideal frailty screening tools for bladder cancer patients.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2020.04.036.

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