# Frailty and outcomes in older cancer patients

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# PREOPERATIVE FRAILTY AND OUTCOME IN PATIENTS UNDERGOING RADICAL CYSTECTOMY

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# ABSTRACT

**Objective**

To determine the value of preoperative frailty screening in predicting postoperative severe complications and 1 year mortality in patients undergoing radical cystectomy.

**Methods**

Prospective cohort single centre study in patients undergoing radical cystectomy from September 2016-December 2017. Preoperative frailty screening was implemented as standard care and was used to guide shared decision making during multidisciplinary team meeting. Frailty screening consisted of validated tools to assess physical, mental and social frailty. Patients were considered frail when having ≥2 frailty characteristics. Primary endpoint was the composite of a severe complication (Clavien Dindo (CD) grade III-V) within 30 days and 1 year all-cause mortality. Secondary endpoints included any complication (CD II-V), length of stay, readmission within 30 days and all-cause mortality. Logistic regression analysis and the concordance statistic were used to describe the association and predictive value of preoperative frailty screening.

**Results**

63 patients were included; 39 patients (61.9%) were considered frail. Preoperative frailty was associated with a seven-fold increased risk for a severe complication or death one year after surgery (adjusted OR 7.36 (95% CI 1.7-31.8) (22 patients). Compared to American Society of Anesthesiologists score and Charlson Comorbidity Index, frailty showed the best model performance (Nagelkerke $R^2$ 0.20) and discriminative ability (c-statistics 0.72, $p<0.01$) for the primary endpoint. After adding frailty to the conventional ASA risk score, the c-statistics improved by 11% ($p<0.01$). Overall survival was significantly worse in frail patients (23.2 months (95% CI 18.7-30.1)) versus non-frail patients (32.9 months (95% CI 30.0-35.9), P=0.01).

**Conclusion**

Frail patients undergoing radical cystectomy are at high risk for postoperative adverse outcomes including death. Preoperative frailty screening improves preoperative risk stratification and may be used to guide patient selection for radical cystectomy.

# INTRODUCTION

Bladder cancer is frequently diagnosed worldwide and a common cause of death. Approximately, 30% of all new diagnosed patients present with muscle invasive bladder cancer.[1] Radical cystectomy is the gold standard for patients with muscle-invasive bladder cancer and patients with recurrent high risk non-muscle invasive disease. [2,3] Although radical cystectomy is a common urologic surgical procedure, postoperative morbidity and mortality rates remain high.[4–6] Especially frail patients with multiple comorbidities seem to suffer from adverse outcomes. [7–9]

Frailty is an age related state of functional decline, characterized by weight loss, muscle wasting and reduced functional capacity. Frailty has been associated with postoperative complications, disability, loss of health related quality of life (HRQL) and decreased cancer survival.[8] With ageing of the population, the incidence of bladder cancer will continue to rise, and physicians will encounter the dilemma of treatment decisions in older and more frail patients. The increasing complexity of the management of frail patients undergoing radical cystectomy, and concerns of adverse outcomes demand accurate preoperative risk assessment.

Current traditional risk assessment tools, such as the American Society of Anesthesiologists (ASA) score or the Charlson Comorbidity Score (CCI) are used to guide selection of surgical candidates. However, these predictors focus primarily on medical comorbidities and do not take frailty characteristics into account. There is an unmet need for a preoperative risk stratification tool, with specific attention for frailty, to identify patients at high risk for poor outcomes. The purpose of this prospective study was to determine the predictive value of preoperative frailty screening on short- and long term postoperative outcomes in patients undergoing radical cystectomy.

# METHODS

*Design*

The current study was a single centre prospective cohort study. In 2016, the St. Antonius Hospital, a large teaching hospital and regional referral centre for uro-oncologic surgery, implemented frailty screening as standard care for patients scheduled for radical cystectomy. The results were discussed in a multidisciplinary team (MDT) meeting, with representatives of the departments of Anaesthesiology and Intensive Care, Urology, Internal Medicine, Medical Oncology and Geriatrics.[10] Since patients were treated according to standard local guidelines, the need for informed consent was waived by the local review board of the ethical committee (Medical research Ethics Committee United, number W17.139). The study was performed in accordance with the principles of the Declaration of Helsinki.

*Patients*

All patients who were scheduled for radical cystectomy between September 2016 and December 2017 in the St. Antonius hospital were eligible for inclusion. All patients were routinely discussed in a multidisciplinary urologic oncology team to determine treatment strategy. Each surgical procedure was performed according to standard clinical practice by two experienced urologists.

*Preoperative frailty screening*

Preoperative frailty screening was performed directly after routine preoperative assessment by an anesthesiology (LV) or internal medicine (EV) resident. Frailty screening was supervised by an anesthesiologist dedicated to preoperative screening, and consisted of validated tools to assess physical, mental and social frailty. Analysis of physical frailty included nutritional status (Mini Nutritional Assessment (MNA), gait speed (Timed to Get up and Go Test (TUGT)), polypharmacy (≥5 medicines), daily functioning (NAGI scale) and grip strength.[11–13] Screening for mental frailty included an assessment of cognition (6-CIT) and HRQL (Short Form 12 (SF-12).[14,15]

To assess social frailty we evaluated a patient's living situation and social support system. Frailty characteristics were considered normal or abnormal according to predefined cut off points based on literature. Patients were considered frail when two or more frailty characteristics were present.

*Clinical characteristics and data collection*

During routine preoperative assessment baseline characteristics, medical history and laboratory tests were routinely collected. Muscle invasive disease was defined as a clinical T stage of ≥T2. To assess the overall weight of comorbidities, the age

adjusted CCI and the ASA classification were calculated for each patient.[16] Data were registered in an electronic database (RedCAP (Research Electronic Data Capture), Vanderbilt University, hosted by St. Antonius hospital).

*Endpoint definitions*

Primary endpoint was the composite of a severe complication (Clavien Dindo (CD) grade III-V) within 30 days after surgery or death after one year. Secondary endpoints were any complication (CD II-V), length of stay, readmission within 30 days after surgery and all-cause mortality. Primary and secondary endpoints were extracted from electronic medical reports. Mortality was collected from the municipal Personal Records Database.

*Statistical analysis*

Data are presented as frequencies and percentages (%) for categorical data, and as median with first and third quartile (IQR) or mean with standard deviation (SD) for continuous data. Normal distribution of the variables was assessed with visual inspection of the histograms and Q-Q plots. Differences between frail and non-frail patients were tested using Chi square test for dichotomous or categorical variables and Mann-Whitney U test or Student's t-test for independent continuous variables.

The association between separate risk scores, individual frailty characteristics and the endpoints were analysed with univariable logistic regression. Because age and tumor stage (muscle invasive versus non-muscle invasive) were a priori expected to be related with the endpoints and the investigated risk scores, all models were adjusted for those variables resulting in adjusted odds ratios (OR) with 95% confidence intervals (CI).

To assess the discriminatory ability of separate risk scores and the added value of frailty, the c-statistic was used. The C-statistic is an index of predictive discrimination, with a value of 0.5 indication random prediction, and a value of 1 indicating perfect prediction. Overall model performance was reported by Nagelkerke's $R^2$. Nagelkerke's $R^2$ ranges from 0 to 1, with higher values indicating better model performance.

Kaplan-Meier curves were used for survival analysis. Differences in Kaplan-Meier curves between frail and non-frail patients were analysed with log-rank test. Finally, cox regression analysis were used to adjust for muscle invasiveness, because patients with muscle invasive disease have a poor prognosis compared to patients with non-muscle-invasive disease.

P-values <0.05 were considered statistically significant. All data analyses were performed using IBM SPSS Statistics for Windows version 22 (IBM Corp. Armonk, NY, USA).

# RESULTS

*Population and outcome*

A total of 64 patients were scheduled for cystectomy and underwent preoperative frailty screening. One patient was excluded, because surgery was abandoned after reassessment of the cancer stage by the pathologist. The final cohort consisted of 63 patients, with a median age of 67 (IQR 61-74) years. Two patients (3.2%) had surgery for non-oncologic diseases: one patient had chronic bladder pain syndrome, and another patient had iatrogenic ureteral injury after rectal amputation.

Of all oncologic patients, 61.9% was diagnosed with muscle invasive disease. Five patients (7.9%) received neo-adjuvant chemotherapy. 24 Patients (38.1%) underwent a robot assisted laparoscopic radical cystectomy with intracorporal urinary diversion. In all other patients a complete open surgical procedure was performed. Twenty-one percent (13/63) of patients was classified ASA ≥3, and median CCI was 5 (4-6). Baseline characteristics of frail and non-frail patients are presented in table 1. Overall, 22 patients (34.9%) had a severe complication or died (CD III-V) within one year after surgery. Any complication occurred in 42/63 patients (66.7%). Fascial dehiscence (5/10 patients) or other acute abdominal signs (caused by rectal, small bowel or urostoma lesions in 3/10 patients) were the most common reasons for reoperation. The operation technique (laparoscopic versus open) was not associated with the occurrence of a severe complication (P=0.34). More than half of the patients (58.7%) were diagnosed with an infection, including eight (8/37) patients with urosepsis. Urosepsis was the most common reason for readmission to the ICU, and readmission within 30 days after discharge. One third (22/63) of patients died within two years.

*Preoperative frailty*

Table 2 presents the prevalence of preoperative frailty characteristics in the study population.

Age of the study population ranged from 45 to 82 years, 3.2% (2/63) of patients were octogenarians. One or more frailty characteristics were present in 52 (82.5%) patients. Physical frailty was more common (51 patients, 81%) than mental or social frailty (38 patients, 60.3%) and 0 patients respectively). Multidomain frailty was present in 39 (61.9%) patients.

Physical frailty consisted primarily of impaired grip strength, anemia or polypharmacy. Of the anemic patients, 2/19 (10.5%) were diagnosed with severe anemia (Hb≤6 mmol/l) and 1/19 (5.3%) developed anemia after neoadjuvant chemotherapy.

**Table 1.** Baseline characteristics (N=63)

| | **Frail patients (N=39) (%)** | **Non-frail patients (N=24) (%)** | ***P*-value** |
|---|---|---|---|
| **Age, mean (±SD)** | 69 (± 8) | 62 (± 8) | <0.01 |
| **Male gender** | 30 (76.9) | 18 (75) | 0.86 |
| **BMI, mean (±SD)** | 25.5 (± 3.5) | 26.4 (± 3.6) | 0.36 |
| **Age adjusted CCI, mean (±SD)** | 5 (± 1.5) | 4 (± 1.1) | <0.01 |
| **ASA classification** | | | <0.01 |
| 1 | 5 (12.8) | 10 (41.7) | |
| 2 | 21 (53.8) | 14 (58.3) | |
| ≥ 3 | 13 (33.3) | 0 (0) | |
| **Comorbidities** | | | |
| Cardiovascular disease | 23 (59) | 16 (41) | <0.05 |
| Pulmonary disease | 8 (20.5) | 0 (0) | <0.05 |
| Diabetes Mellitus | 4 (10.3) | 2 (8.3) | 1.00 |
| Renal failure (GFR <60) | 7 (17.9) | 1 (4.2) | 0.14 |
| Stroke | 4 (10.3) | 1 (4.2) | 0.64 |
| **Intoxication** | | | |
| Current smoking | 18 (46.2) | 2 (8.3) | <0.01 |
| Alcohol use* | 11 (28.2) | 4 (16.7) | 0.30 |
| **cT stage** | | | 0.42 |
| Muscle-invasive | 26 (66.7) | 13 (54.1) | |
| Non-muscle-invasive | 14 (35.9) | 13 (54.2) | 0.35 |
| Lymph node positive | 9 (23.1) | 3 (12.5) | 1.00 |
| Non-oncological | 1 (2.6) | 1 (4.2) | |
| **Neoadjuvant chemotherapy** | 4 (10.3) | 1 (4.2) | 0.64 |
| **Type of surgery** | | | 0.65 |
| Robot cystectomy | 14 (35.9) | 10 (41.7) | |
| Open cystectomy | 25 (64.1) | 14 (58.3) | |

Abbreviations: SD: standard deviation; CCI: Charlson Comorbidity Score; ASA: American Society of Anesthesiologists; cT: Clinical T stadium. *woman >2 units/day, men>3 units/day

Median number of prescriptions were 3 (1-5) and 20 (31.7%) patients had ≥5 prescribed medications. Mental frailty was characterized by loss of HRQL; more than half of the patients reported a HRQL below the population mean. None of the patients were considered frail on social domain. Although 20% of the patients lived alone, all patients had a strong social support system. Overall, 39 patients (61.9%) were considered frail (≥2 frailty characteristics).

**Table 2.** Frailty characteristics (N=63)

| Variable | Score range | Cut off point for frailty | Median (IQR) | Number of frail patients (%) |
|---|---|---|---|---|
| **Age** | 0-inf | ≥ 75 years | 67 (61-74) | 14 (22.2) |
| **6-CIT** | 0-28 | ≥ 6 | 0 (0-2) | 5 (7.9) |
| **SF-12 PCS (N=54)** | 0-100 | < 50 | 51.5 (42.2-55.7) | 26 (48.1) |
| **SF-12 MCS (N=54)** | 0-100 | < 50 | 47.4 (42.6-51.3) | 37 (68.5) |
| **NAGI** | 0-7 | ≥ 3 | 0 (0-0) | 4 (6.3) |
| **MNA** | 0-30 | ≤ 7 | 11 (9-11) | 8 (12.7) |
| **TUGT** | 0-inf | ≥ 10 sec | 8.6 (7.58-9.80) | 13 (20.6) |
| **Grip strength** | 0-inf | Age dependent | - | 20 (31.7) |
| **Polypharmacy** | 0-inf | ≥ 5 drugs | 3 (1-5) | 20 (31.7) |
| **Anemia** | 0-11 | < 8 mmol/l | 8.6 (7.6-9.1) | 19 (30.6) |
| **Living alone** | Yes-no | - | - | 20 (31.7) |
| **At home with home care** | Yes-no | - | - | 6 (9.5) |
| **No social support system** | Yes-no | - | - | 0 (0) |

Abbreviations: IQR, Interquartile Range; 6-CIT, 6 Item Cognitive Impairment Test; SF-12, Short Form Health Survey; PCS, Physical Component Summary; MCS, Mental Component Summary; MNA, Mini Nutritional Assessment; TUGT, Timed to Get and Go test; inf, infinity

*Preoperative frailty and outcome*

A severe complication or death after one year was more common in frail patients (48.7% versus 12.5% in non-frail patients, P<0.01) (Table 3). After adjustment for age and muscle invasiveness preoperative frailty was associated with a seven-fold increased risk for a severe complication or death after one year (Table 4). Compared to ASA and CCI, frailty showed the best model performance, and discriminative ability for the primary endpoint. After adding frailty to the conventional ASA risk score, the discrimination slope increased by 11% (c-statistic 0.75, p<0.01). Individual frailty characteristics were not associated with the primary or secondary endpoints. Of all frailty characteristics, polypharmacy showed the best model performance (Nagelkerke $R^2$ 0.08).

After a median follow up time of 26 (IQR 14-31) months, overall survival was worse in frail patients (mean 23.2 months (95% CI 18.7-30.1) versus 32.9 months (95% CI 30.0-35.9) for non-frail patients (P=0.01); Figure 1) Overall survival was worse for patients with muscle invasive disease (22.8 months (95% CI 18.2-27.5)) compared to patients with non-muscle invasive disease (32.3 months (95% CI 28.9-35.8), P<0.01. Frailty remained associated with worse overall survival after adjustment for muscle invasiveness (adjusted HR 3.2 (95% CI 1.1-9.4), P=0.04.

**Table 3.** Post-operative outcomes (N=63)

| | Frail patients (N=39) (%) | Non-frail patients (N=24) (%) | *P*-value |
|---|---|---|---|
| **Severity of complications** | | | 0.30 |
| Clavien Dindo II | 16 (41) | 12 (50) | |
| Clavien Dindo III | 4 (10.3) | 3 (12.5) | |
| Clavien Dindo IV | 4 (10.3) | 0 (0) | |
| Clavien Dindo V | 3 (7.7) | 0 (0) | |
| **Reoperation** | 9 (23.1) | 1 (4.2) | 0.07 |
| **Inplanned ICU admission** | 7 (17.9) | 0 (0) | 0.04 |
| **Length of stay, median (IQR)** | 14 (11-27) | 13 (11-16) | 0.21 |
| **30 days mortality** | 3 (7.7) | 0 (0) | 0.28 |
| **Readmission within 30 days** | 5 (12.8) | 3 (12.5) | 1.00 |
| **Required new home care or residential care after surgery** | 29 (74.4) | 19 (79.2) | 0.66 |
| **1 year mortality** | 12 (30.8) | 1 (4.2) | 0.01 |
| **2 year mortality** | 18 (46.2) | 4 (16.7) | 0.02 |

Abbreviations: IQR: Interquartile Range; ICU, Intensive care Unit

**Table 4.** Results of risk scores and components of the preoperative frailty screening on the prediction of severe complications and 1 year all-cause mortality.

| Model | OR (95% CI)* | *P*-value | Nagelkerke $R^2$ | C-statistic* | *P*-value |
|---|---|---|---|---|---|
| **Single risk score** | | | | | |
| *ASA score (<3, ≥3)* | 4.28 (1.13-16.17) | 0.03 | 0.12 | 0.64 | 0.07 |
| *CCI score (<5, ≥5)* | 1.53 (0.45-5.19) | 0.49 | 0.03 | 0.57 | 0.37 |
| *Frailty model (<2, ≥2)* | 7.36 (1.70-31.84) | <0.01 | 0.20 | 0.72 | <0.01 |
| **ASA + frailty model** | 3.58 (1.52-8.41) | <0.01 | 0.22 | 0.75 | <0.01 |
| **Frailty characteristics** | | | | | |
| *Polypharmacy* | 2.72 (0.88-8.45) | 0.08 | 0.08 | 0.63 | 0.09 |
| *Anemia* | 1.39 (0.44-4.40) | 0.57 | 0.03 | 0.59 | 0.27 |
| *6-CIT* | 1.28 (0.20-8.37) | 0.80 | 0.02 | 0.56 | 0.47 |
| *TUGT* | 2.55 (0.70-9.33) | 0.16 | 0.06 | 0.62 | 0.12 |
| *Hand grip strength* | 1.89 (0.63-5.73) | 0.26 | 0.05 | 0.59 | 0.27 |
| *NAGI* | 1.95 (0.25-15.14) | 0.52 | 0.03 | 0.57 | 0.35 |
| *MNA* | 2.05 (0.46-9.25) | 0.35 | 0.04 | 0.60 | 0.20 |
| *SF12 PCS* | 1.83 (0.63-5.31) | 0.27 | 0.05 | 0.61 | 0.17 |
| *SF12 MCS* | 0.43 (0.15-1.26) | 0.12 | 0.07 | 0.63 | 0.10 |
| *Living alone* | 0.98 (0.32-3.00) | 0.97 | 0.02 | 0.55 | 0.50 |

Abbreviations: CCI: Charlson Comorbidity Score; ASA: American Society of Anesthesiologists; 6-CIT, 6 Item Cognitive Impairment Test; SF-12, Short Form Health Survey; PCS, Physical Component Summary; MCS, Mental Component Summary; MNA, Mini Nutritional Assessment; TUGT, Timed to Get up and Go Test. *All models were adjusted for age and muscle invasiveness

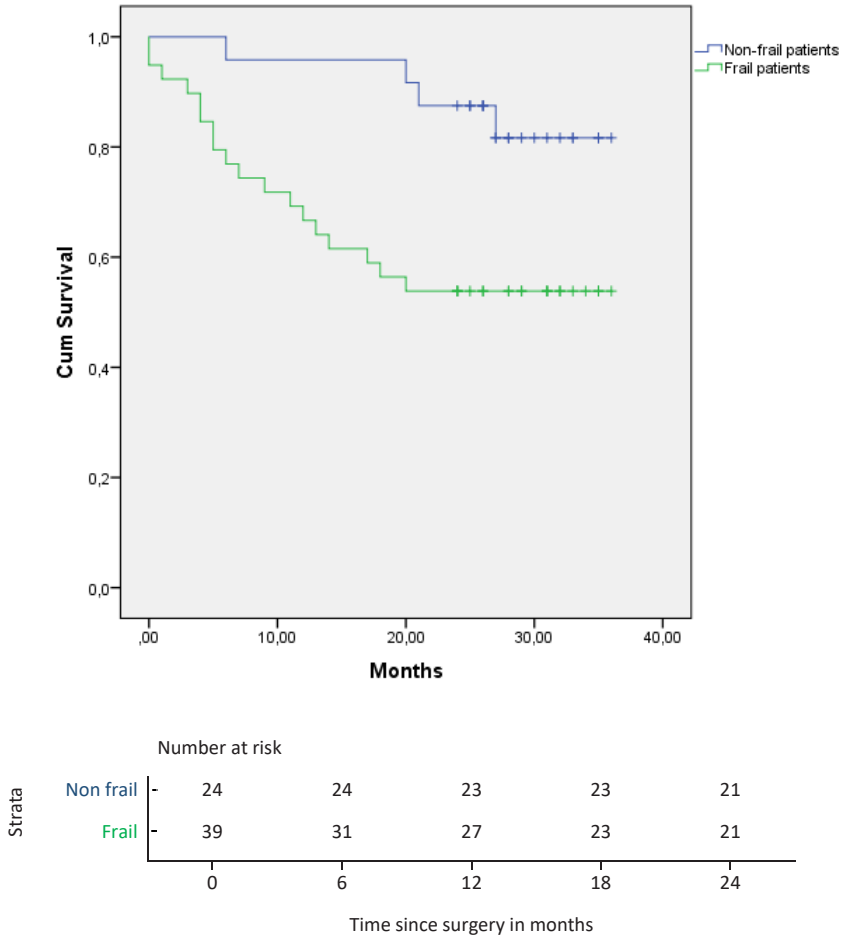


**Figure 1.** Kaplan meier plot for frail versus non-frail patients.

# DISCUSSION

This study determines the value of preoperative frailty screening to predict postoperative severe complications and one year all-cause mortality in patients undergoing radical cystectomy. Frailty was commonly present and associated with a seven-fold increased risk of severe postoperative adverse outcomes, including one year mortality. Furthermore, preoperative frailty screening improved risk prediction for severe complications or death one year after surgery, and may be useful for preoperative shared decision making in patients scheduled for radical cystectomy.

Although radical cystectomy provides the best long term oncological prognosis in muscle invasive- and recurrent high risk non-invasive bladder cancer, surgical morbidity and mortality are high. Especially in frail patients, radical cystectomy has been associated with poor postoperative outcomes. [7–9,17–19]



Contemporary series from high volume centres report complication rates that range from 25-80%, with major complications occurring in approximately one third of the patients.[4,5] Furthermore, comparable results of 30 days mortality (2-4%) and long term mortality (5 years overall survival 42-58%) were observed in several other studies. [6,19,20] As presented in our study, frailty is common in patients scheduled for radical cystectomy. [8] In our cohort the majority of patients had at least one frailty characteristic and two-third of patients were frail in two out of three domains. This can be expected in a population which is characterized by older age and multimorbidity. Bladder cancer patients have the highest median age at time of diagnosis in all types of cancers and a median of eight chronic comorbidities, compared to a median of four in the general population. [21] As older age and comorbidities are often associated with frailty, it seems essential to take frailty characteristics into account in order to make the right treatment decisions in the growing cohort of patients undergoing radical cystectomy.

A majority of the patients is willing to undergo surgical treatment for bladder cancer when risk of adverse outcome is acceptable. Information on expected changes in daily functioning and quality of life after surgery is more likely to influence preoperative decision making than the often limited cancer related overall survival. However, this type of outcome data in frail patients with bladder cancer is currently lacking, which makes risk stratification complicated. Besides that, preoperative risk management consist of traditional risk assessment tools, such as the American Society of Anesthesiologists (ASA) score or the Charlson Comorbidity Score (CCI) and do not take frailty characteristics into account, leading to an underestimation of perioperative risk. The majority of the studies that examine frailty in patients undergoing radical cystectomy are population

based, single centre historical cohort studies.[8] Most studies use the simplified Frailty Index or the Modified Frailty index, which are solely based on functional status and comorbidities.[7,17,18,22] Prospective studies that cover all frailty domains (physical, mental and social), such as our study, are scarce. In one prospective study of 123 bladder cancer patients the Fried Frailty Criteria were predictive of high-grade complications.[19] Our study results showed that an assessment of frailty in multiple domains was strongly associated with adverse outcome, and that adding frailty to the ASA classification improved discrimination for the primary outcome by 11%.

In addition to an improved preoperative risk stratification, frailty screening has the ability to identify potentially modifiable risk factors. Considering that frailty is associated with adverse outcome, it seems reasonable to focus on prehabilitation in order to reduce postoperative complications. However, it is uncertain if prehabilitation is effective in decreasing postoperative outcomes in high risk patients. A recent randomized controlled study of seventy patients undergoing a radical cystectomy concluded that multimodal prehabilitation resulted in faster functional recovery after surgery.[23] In contrast, preoperative exercise-based programs failed to show significant improvement in physical and surgical outcomes.[24] Additionally, a preoperative risk profile that includes frailty may contribute to shared decision making by better informing the surgeon and patient on risk of adverse outcomes.

High risk patients may be better candidates for bladder-sparing approaches, such as (chemo)radiation.[25] In order to optimize preoperative shared decision making and to ensure the complexity of the management of frail patients, a MDT approach can be beneficial in the development of such patient-centered treatment plan.[10] Due to the absence of high quality outcome data in frail patients, clinical consensus in the form of a MDT approach (experienced based medicine) may the best available evidence to guide patient selection for radical cystectomy.

The following limitations should be considered. Although data were prospectively and consecutively collected, our sample size is limited. As a result we were unable to determine which individual frailty characteristics were most strongly associated with adverse outcome. As a full frailty screening is time consuming, a short frailty screening would improve its applicability in daily practice. Although a clear recommendation cannot be made based on our data, we would suggest the use of a screening tools that cover both the physical and mental domains of frailty. Furthermore, to avoid overfitting the multivariable analysis we were not able to add more variables such as operation technique. This also applies for the cox regression analysis where we adjust only for muscle invasiveness while variables such as older age, smoking and N+ stage may have influenced survival.

Finally, information on the long term cause of death was not available, which makes it impossible to distinguish between non cancer – and cancer related survival. However, frailty remained associated with one year mortality after adjustment of tumor stage in the cox regression analysis. Despite these limitations, this study showed a detailed overview of one year of experience in multidomain frailty screening and adds important information on risk prediction of frail patients undergoing radical cystectomy.

In conclusion, our study confirmed that frailty is common in patients undergoing radical cystectomy and strongly associated with severe complications and all-cause mortality. Preoperative frailty screening has the ability to improve risk stratification and may be used to guide patient selection for radical cystectomy. However, larger prospective trials are necessary to confirm our findings.

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