Can we lower the rates of cystectomy complications by modifying risk factors? A review of the literature

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Citation: Hladun T, Ratajczak J, Salagierski M. Can we lower the rates of cystectomy complications by modifying risk factors? A review of the literature. Cent European J Urol. 2022; 75: 28-34.

Introduction
Radical cystectomy (RC), beyond its therapeutic effect, is associated with significant rates of complications, hospital readmissions and mortality. In recent years much research has been made in order to clarify the main reasons of these events. This article, based on a literature review, presents the impact of risk factors on RC complications and highlights possible modifications of these factors to reach better RC outcome.

Material and methods
PubMed, Science Direct, Google Scholar databases were searched using keywords to identify studies about risk factors and RC complications between 2010 and 2021. A total of 96 articles were retrieved and studied as full-text versions. The most significant data was targeted, analysed and categorized according to the article’s design.

Results
All the most valuable risk factors of RC complications were grouped in patient-related, treatment-related risk factors and subgrouped in nonmodifiable, modifiable and potentially modifiable categories. All the modifiable and potentially modifiable risk factors were found to have considerable value, as their adjustment lowers the rates of morbidity and mortality.

Conclusions
Proper identification and adjustment of the risk factors present the possibility of better RC results. Although, in advanced disease and highly morbid cases, complications are not fully omitable. Management of bladder cancer (BC) in high-volume centres using new technologies offers lower rates of complications. To sum up, rigorous interdisciplinary presurgical patient preparation should be implemented in BC management.

Key Words: risk factors • radical cystectomy • complications • bladder cancer

INTRODUCTION
Bladder cancer (BC) is the 10th most common cancer in the world, and its incidence is steadily rising worldwide, especially in developed nations. Radical cystectomy (RC) based treatment remains the gold standard for patients with muscle-invasive bladder cancer (MIBC, T2-T4a N0M0) [1]. Additionally, RC is also indicated in patients with recurrent or progressive non-muscle invasive bladder cancer. Besides the therapeutic effect RC is associated with significant rates of complications, hospital readmission, and mortality. Approximately 30% of patients experience postoperative complications within 30 days of surgery and 60% of patients experience complications within 90 days of the procedure [2]. Postoperative complications are in most cases defined and classified according to the Clavien–Dindo classification as suggested by international guidelines (Table 1). Common complications include gastrointestinal (30%), infectious (25%), wound and stoma (15%), upper urinary tract (11%), cardiovascular (11%) and venous thromboembolism (8%) [2]. A variety of risk factors can impact the incidence of RC complications. In this review, we wanted to highlight the most meaningful risk factor. Therefore,
due to the nature of these factors we divided them into patient-related and treatment-related. The majority of patients undergoing RC are already in conditions with numerous risk factors that cannot be changed. But there are certain factors that doctors can impact before or during the planned RC. Consequently, we grouped the risk factors into modifiable and nonmodifiable. We described the modifiable factors with particular attention to their clinical merit.

RC complications prolong a patient’s length of stay in the hospital, increase total cost of treatment, and diminish quality of life thus any actions that possibly lower the rates of these complications are important.

**Literature search**

A systematic literature search was performed using PubMed, Science Direct, Google Scholar databases to identify reviews and studies on BC risk factors and RC complications between 2010 and 2021. In order to obtain specific data, the following main key words and their combinations were used: risk factors, radical cystectomy, comorbidities, complications, bladder cancer. Only literature discussing human studies was considered. Altogether, >200 references were screened by considering the headline and the abstract, and 40 articles were retrieved and studied as full-text versions. Hence after the articles were reviewed, the most significant data was targeted, analysed and categorized according to the article’s design.

**Methodology**

In this study based on a literature review, we grouped all the most valuable risk factors of RC complications in categories: patient-related, treatment-related (Figure 1).

We grouped the patient-related risks to nonmodifiable, modifiable and potentially modifiable categories. Nonmodifiable group consists of factors that cannot be altered before RC. Factors that can be altered in any time with positive effect by patient or doctor comprise the modifiable group. Potentially modifiable group consists of risk factors that are hard to adjust due to their congenital, chronic or advanced status.

All the treatment-related risk factors were grouped as modifiable or potentially modifiable. Modifiable group risk factors are usually dependable on doctors’ choice and can be altered pre- or intraoperatively. Other risk factors that at certain circumstances are

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**Figure 1. Risk factors of radical cystectomy complications.**

- **Patient-related**
  - Nonmodifiable: Gender, Age, Race, Previous radiotherapy, CKD
  - Potentially modifiable: Mental status, DM, CVDs, PDs, Chronic steroid therapy, Tumour stage and grade
  - Modifiable: Nutritional status, Smoking status, Anaemic status

- **Treatment-related**
  - Modifiable: NAC, Surgical approach, UD type, Abdominal wall closure technique
  - Potentially modifiable: Perioperative blood loss and transfusion, Operative time length

CKD – chronic kidney disease; DM – diabetes mellitus; CVDs – cardiovascular diseases; PDs – pulmonary diseases; UD – urinary diversion; NAC – neoadjuvant chemotherapy
hard to adjust or omit were grouped as possibly modifiable. The nonmodifiable factors are only casually described as long as there are no probabilities to adjust them. All the modifiable and potentially modifiable risk factors are rigorously defined in order to show their clinical value.

RESULTS

Patient-related nonmodifiable group

Gender, age, race, previous pelvic radiotherapy (RT), chronic kidney disease (CKD) comprise this group. There are several notable issues about these factors described in recent studies. Some papers conclude that female gender is related with higher probability of infectious and cardiac complications within 6 months after RC [3, 4]. Reports show that elderly patients usually present with more advanced tumour stages at RC which defines the rates of early and late postoperative complications as well as early morbidity [5, 6, 7]. Recently, clinical significance of race on postoperative outcomes and identify patients can provide additional information useful in predicting postoperative outcomes and identify patients in need of psychological or pharmacological treatment. The mechanism of association between BC and diabetes mellitus (DM) remains unclear. It is considered that DM can impact the outcome of any major surgery. A number of studies have considered a positive association between diabetes and incidence of post-RC complications [16]. But are there differences in complication rates between patients with controlled DM (CDM) and uncontrolled DM (UDM). Faiena et al. [17] found in their study that postoperative surgical site infections (SSI), respiratory and paralytic ileus complications, as well as mortality were significantly more common in the UDM than in the CDM groups. Although DM is uncurable, we still placed this risk factor into the potentially modifiable group, as proper presurgical adjustment of UDM lowers the rates of potential RC complications.

Patient-related potentially modifiable group

Mental status impairments are common among seniors and may include isolation, affective and anxiety disorders, dementia, and psychosis, among others. Studies show a relevant association between patient reported baseline mental health and high-grade early and late complications after RC [14]. Psychological factors have been shown to independently worsen patient morbidity and mortality rates but can be modified. Geoffrion et al. [15] highlighted the importance of holistic preoperative medical care, patient education, presurgical pharmacological treatment and adjustment of sleep disorders to potentially optimize surgical outcomes for patients with mental impairments. Altogether, preoperative patient assessment of mental status through validated questionnaires can provide additional information useful in predicting postoperative outcomes and identify patients in need of psychological or pharmacological treatment. The mechanism of association between BC and diabetes mellitus (DM) remains unclear. It is considered that DM can impact the outcome of any major surgery. A number of studies have considered a positive association between diabetes and incidence of post-RC complications [16]. But are there differences in complication rates between patients with controlled DM (CDM) and uncontrolled DM (UDM). Faiena et al. [17] found in their study that postoperative surgical site infections (SSI), respiratory and paralytic ileus complications, as well as mortality were significantly more common in the UDM than in the CDM groups. Although DM is uncurable, we still placed this risk factor into the potentially modifiable group, as proper presurgical adjustment of UDM lowers the rates of potential RC complications.

Cardiovascular diseases (CVD) play a significant role in major surgery outcome. Previous and current vein thrombosis disease, atrial fibrillation, arterial hypertension (AH), previous myocardial infarction and past cardiac surgery increase the risk of intraoperative
and short postoperative complications after RC [3]. Reports show that diastolic dysfunction (E/e' >15) is related with major adverse cardiac events (MACE) within 6 months after RC [4, 18]. Therefore, cautious pre-surgery workup involving the cardiologist must be made with CVD patients to lower the rates of any grade complications as well as morbidity after RC. Pulmonary diseases (PD) include asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, pneumonia, and lung cancer. Patients with PD are classically underweight, malnourished, have poor pulmonary reserve, and poor exercise tolerance. Tolchard et al. [19] report that patients with poor cardiopulmonary exercise testing results (anaerobic threshold ≤11 mL/kg/min and a VE/VCO2 of ≥33) and presence of AH have longer period of stay in hospital and higher odds of complications by 90 days after RC. COPD together with other comorbidities increases the risk of postoperative pulmonary complications after RC [20]. Sayyid et al. [10] report that patients with COPD have a 2.33-fold increased risk of re-operation after RC. Majority of researchers agree that preoperative treatment, rehabilitation and exercise programs for patients with PD should be proposed in an effort to optimize respiratory status and lower the rates of RC complications.

After reviewing the studies, we found that complication rates may vary depending on dose and duration of steroid use. Ismael et al. [21] in their major study found that superficial SSIs increased from 2.9% to 5%, deep SSIs increased from 0.8% to 1.8%, organ/space SSIs and dehiscence increased 2 to 3-fold and mortality increased almost 4-fold in patients on preoperative long-term steroid therapy compared to the no steroid population. Wang et al. [22] reported that high-dose corticosteroid administration for <10 days has no clinically important effect on perioperative complications. However, in patients taking chronic corticosteroids for at least 30 days before surgery they found 2 to 5 times increased rates of wound complications compared with those not taking corticosteroids. Can we modify this risk factor? Given the significant impact on surgical outcome of chronic steroid abuse, it should be evaluated and, if possible, the dosage should be addressed or excluded under the therapeutic custody prior to surgery. More advanced BC disease demands more complex treatment and lowers the rates of positive outcome. Association between stage and grade of the tumour with higher incidence of early complications and mortality after RC is described in recent studies [5, 7]. However, research by Zainfeld et al. [13] found no significant differences in pathologic stage, age and other comorbidities regarding 30-day complications or readmission. The only possibility to alter the preoperative tumour stage is neoadjuvant chemotherapy (NAC). Research by Petrelli et al. [23] shows that NAC is positively involved in BC pathological downstaging. Assessing the disparity of results shown in latest studies we believe that NAC should be recommended in suitable patients to adjust the rates of RC complications.

**Patient-related modifiable group**

Malnutrition is the condition that develops when the body is deprived of vitamins, minerals and other nutrients it needs to maintain healthy tissue and organ function. The main malnutritional conditions that impact RC outcome are obesity and undernutrition states, such as sarcopenia or hypoalbuminemia. High-grade Clavien Dindo RC complications frequently come up within the obese population and consequently increase the rates of reoperation or early mortality [6, 10]. A study by Ornaghi et al. [24] found that patients with body mass index (BMI) 25–29.9 kg/m2 had a 1.5-fold increased risk of 30 day overall complications, whereas patients with BMI ≥30 kg/m2 had almost a double increased risk. Other evidence claims that class I–III obesity and preoperative hypoalbuminemia (<3.5 g/dL) were independently associated with increased risk of moderate-severe complications and mortality within 30 and 90 days of RC [25]. Pre- and perioperative physical activity, proper nutrition, pharmacological treatment are suggested to modify malnutrition states. Recent data reveals that preoperative nutritional status correction lowers the possibility of RC complications and mortality.

Current smoking status and high cumulative smoking exposure at time of RC are associated with advanced tumour stage, nodal metastasis, disease recurrence, and cancer-specific mortality in patients treated with RC [26]. Therefore, studies report that smokers at the time of RC are significantly associated with a two-fold increase in postoperative complications, particularly wound dehiscence and myocardial infarction, following radical cystectomy compared with non-smokers [26]. While smoking status should not preclude, or even delay surgery, there are high-quality evidences that suggest that even a short-period of cessation could improve outcomes. Research by Sathianathen et al. [27] reports that active smoking status modified by counselling and nicotine replacement therapy that commenced four weeks prior to surgery and continued for four weeks after, had a 49% [95% CI 3–73] relative risk reduction in RC complications compared to controls without this adjustment. Hence, smoking cessation
should be encouraged during bladder cancer workup to optimize surgical outcomes. Recently, there has been increasing interest in the role of anaemic status as a prognostic factor in surgical outcomes after RC. High circulating oxygen transport capacity has higher impact compared to other factors like duration of surgery, tumour stage, or oral anticoagulation for incidence of perioperative blood transfusion (PBT) [28]. A study by Pavone et al. [29] showed that preoperative anaemia condition is very common in patients with MIBC and is proved to be a predictor of postoperative complications, but not of 90-day mortality. In order to optimize the RC outcome, patient blood management programs during prehabilitation should be implemented to modify the anaemic status. This data further emphasizes the importance of a solid preparation of patients with altered anaemic status.

**Treatment-related potentially modifiable group**

Significant perioperative blood loss (PBL) and perioperative blood transfusion are clinically relevant and prognostically important events in perioperative care. Researchers report that PBT accompanied with other comorbidities are found to play significant role of complications after RC [30]. A study by Parker et al. [31] stated that approximately 25% of patients undergoing RC with PBT experience an infection within 30 days of surgery. Further reports demonstrated that myocardial injury occurred in 14.1% of patients with incidence of PBL and PBT during RC [32]. Due to the emerging role of PBL in RC complications, surgeons should be encouraged to cooperate closely with the anaesthesiologic unit and cautiously perform the surgeries, if possible, using available new technologies and haemostatic agents to decrease the rates of needless PBT.

After decades of research there is evidence that operative time length (OTL) is an independent and potentially modifiable risk factor for complications. Cheng et al. [33] in their study found that there is a positive association between the OTL and complications such as SSI, venous thromboembolism (VTE), PBL, hematoma formation, and necrosis. Other studies also reported higher rates of complications after RC in patients with longer OTL and higher age [3, 31]. Taking into account the adverse consequences of complications, decreased OTL should be a universal goal for surgeons, hospitals, and policy-makers. We must recognise that there are a number of states like altered anatomy after previous surgery and RT or obesity that make RC more challenging. In these cases PBL, PBT and prolonged OTL may not be omittable.

**Treatment-related modifiable group**

Neoadjuvant chemotherapy (NAC) is one of the most relevant risk factors from this group. Is there a role of NAC in RC complications and early mortality? High-evidence studies show that NAC administration is not associated with higher rates of short-term complications and mortality after RC [13, 34]. However, other researchers found that receipt of NAC significantly decreased both 30- and 90-day complication rates after RC [5, 30]. Positive impact of NAC on pathologic tumour downgrading was noted before [23]. Administration of NAC is highly dependable on patients overall health status, in particular renal function. Thus, presurgical patient preparation in tight oncological cooperation is needed to identify the eligible patients. Surgeons must be aware of higher probability of complications after RC in patients without receipt of NAC.

RC can be performed as an open (ORC), laparoscopic (LRC), or robot-assisted surgery (RARC). Usually the choice of surgical approach predetermines other major risk factors as PBL or OTL. Data shows that patients who underwent LRC lost less blood than those with ORC (mean 380 ml, range 317–582 ml vs mean 710 ml, range 595–870 ml, respectively) [35]. RARC studies estimated blood loss during RARC is significantly lower than in patients undergoing ORC, but OTL is longer [36, 37]. The study by Adamczyk et al. [36], showed that the ORC group had more severe complications (Grade 2/3) than those in the LRC/ RARC groups. LRC and RARC are an equivalent treatment to ORC in terms of oncological efficacy and are advantageous in terms of transfusion rates and hospital stays, but not in terms of OTL and overall safety. However, Cusano et al. [37] reported no significant difference in the incidence of post-operative complications (≤90 days postsurgery) between ORC and RARC surgical groups. In conclusion, the choice of surgical approach should be based on thorough BC case evaluation and surgeon’s expertise, without compromising the safety of the patient.

Does urinary diversion (UD) have an impact on RC outcome? The main methods of UD are ileal conduit (IC), orthotopic neobladder (ONB), or simple ureterocutaneostomy (UCS). All of these UD types can be performed intraperitoneally. Zhang et al. [38] found that intracorporeal UD cases had lower PBL, shorter hospitalization and a lower ileus rate than extracorporeal UD and ORC cases. In an alternative study, ONB had the highest probability of postoperative anaemia [35]. However, some authors showed that overall, low- and high-grade 30- and 90- day complications occur at the similar
rates with IC and ONB [13, 36]. Though Korkes et al. [39] in their study report that UCS is a safer alternative for elderly and more frail patients, because it is associated with faster surgery, less PBL, lower PBT rates, lower necessity of intensive care and shorter hospital stay. Lastly, UD strongly matches up with RC approach and surgical decision.

We also added a relatively less recognized risk factor of abdominal wall closure technique to this group. Early postoperative period after open surgery can be complicated by acute wound failure (AWF) such as wound dehiscence. The incidence of abdominal wound dehiscence ranges from 0.25–3% with an associated mortality of up to 25% and is most often seen at around 1 week post-surgery. The optimal choice for closing a typical RC midline incision is using a ‘small steps’ technique of continuous suturing with a slowly absorbable (polydioxanone) suture material in a wound-suture ratio of minimum 1 : 4 with avoidance of excessive tension. Studies show that this technique reduces the rates of AWF [40].

All of the treatment-related risk factors are strongly associated with the hospital volume and surgical experience. The high-evidence study of Maibom et al. [6] reported that the risk of postoperative complications and mortality after RC was decreased by 45% when performed at a high-volume centre compared with a low-volume centre. The European Association of Urology (EAU) Muscle-Invasive and Metastatic Bladder Cancer Guideline Panel recommends RC to be performed at centres with at least 10 RC/year and preferably >20 RC/year. To finish, we believe that modification of the treatment-related risk factors depends on the complexity of each BC case and surgical expertise; data shows that proper modification lowers the risks of RC complications.

CONCLUSIONS

Up to now doctors have used a variety of risk stratification tools that anchor on a patient’s risk factors, though these tools are lacking all of the risk factors we found to be impactful. We believe risk factors should be grouped for better understanding of their origins and modification possibility. We highlighted the importance of modifiable and potentially modifiable risk factors. This review also shows that proper modification of these factors may lead to lower rates of RC complications and mortality. Attention is also called upon the close collaboration between medical specialties and importance of high-volume BC centres for achieving better RC outcome. More research should be made in order to clarify the role and modification possibility of known RC complications risk factors as well as spotting new ones. The prospect of better RC outcome by adjustment of known risk factors should be recognised by doctors.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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