

# How to lower postoperative complications after radical cystectomy – a review

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**Introduction** Lowering morbidity and mortality after RC is subject of considerable interest. Lately, many evidence-based data on improvements in operative technique, anesthetic management, and patient care have been published.

In this article, we present a review of literature on how to lower postoperative complications after RC.

**Material and methods** The Medline, and Web of Science databases were searched without a time limit on February 2016 using the terms ‘cystectomy’ in conjunction with ‘radical’, ‘bladder cancer’, ‘complications’ or ‘management’. Boolean operators (NOT, AND, OR) were also used in succession to narrow and broaden the search. The search was limited to the English, Polish and Spanish literature.

**Results** Many complications may be avoided by appropriate patient selection and meticulous introduction of care protocols.

**Conclusions** RC as treatment free of complications, even in the hands of an experienced urologist, does not exist. A large number of complications are acceptable in the name of good long-term results. Optimum results are possible with proper surgical technique, good patients and urinary diversion selection and proper patient management in the pre-, peri, and postoperative period.

**Key Words:** bladder cancer ↔ complications

## INTRODUCTION

Radical cystectomy (RC) is the gold standard treatment for muscle-invasive bladder cancer. According to the EAU Guidelines RC can be also proposed to those patients with non-muscle-invasive tumours who are at the highest risk of progression and to patients with BCG-refractory tumours. Standard RC consists of the removal of the bladder, prostate, seminal vesicles, distal ureters, and regional lymph nodes in men, and the bladder, urethra, adjacent vagina, uterus, distal ureters, and regional lymph nodes in women [1]. Lowering morbidity and mortality after RC is the subject of considerable interest. Lately, many evidence-based data on improvements in the operative technique, anesthetic management, and patient care have been published.

In this article we present a review of literature on how to lower postoperative complications after RC.

## MATERIAL AND METHODS

The Medline, and Web of Science databases were searched without time limit in the February 2016 using the terms ‘cystectomy’ in conjunction with ‘radical’, ‘bladder cancer’, ‘complications’ or ‘management’. Boolean operators (NOT, AND, OR) were also used in succession to narrow and broaden the search. Autoalerts in Medline were also run, and reference lists of original articles, review articles, and book chapters were searched for further eligible articles. The search was limited to the English, Polish and Spanish literature. Prospective and retrospective trials, as well as review articles, were included. Articles that did not address the topics were

excluded, and the full text of the remaining articles was reviewed. A total number of 65 papers was analysed.

RC, especially when performed as a palliative or salvage treatment, is associated with significant complication rates, perioperative mortality and hospital readmission rates. Complications can occur because of complex nature of the surgery and/or performed urinary diversion, but may also be dependent on the patient's comorbidities.

In the last several decades, the total RC mortality has decreased from 40% to less than 4% and the perioperative mortality rate has diminished from 20 to less than 2% [2]. Despite the continuous decline in the incidence of severe complications, they currently concern about 30% of patients during hospital stay and up to 60% of patients within 90 days after laparoscopic and open surgery [2–10]. In case of procedures with the robotic assistance, the total number of complications is similar, with a lower blood loss and transfusion requirements [11, 12]. The most common complications include malfunctioning of the digestive tract (30%), infections (25%), complications associated with wound and stoma (15%), upper urinary tract disorders (11%), cardiovascular complications (11%) and venous thromboembolism (8%) [13]. Additionally, many metabolic changes such as bowel dysfunction, malabsorption of various vitamins, acid-base imbalances, electrolyte imbalances, abnormalities in bone metabolism, formation of renal calculi, and disturbances in the kidney or liver function are observed. Metabolic complications occur, because of the prolonged contact of urine with normally functioning bowel epithelium. Additionally, the length of bowel is shortened and the reabsorption area is diminished [14].

Complications prolong the total length of stay (LoS) in a hospital, and significantly increase total treatment costs. Interestingly, some authors state, that the incidence of complications that occurred within a year period after the operation, has no effect on patients' Health Related Quality of Life (HRQoL) [15].

### Complications reporting

An accurate and reliable complication reporting is essential in order to critically evaluate procedures, improve qualification protocols and compare different methods and center results.

The first attempt to standardize complications after RC reporting was presented in 2009 in the Memorial Sloan Kettering Cancer Centre [16]. The authors proved, that when specific guidelines for the classification of complications are applied, frequency of complications turns out to be higher than in the reports, which do not use unified classification methods [13].

Currently, the Clavien-Dindo classification is the most widely used surgical complication evaluation system [17] (Table 1).

Additionally, while reporting complications, every report should provide key information, such as method of data collecting (retrospective/prospective), duration of follow-up, hospitalization time, outpatient information (events following discharge), definition of complication, mortality and morbidity rate, cause of death, total number of complications, LoS and consideration of comorbidity/risk factors (ASA, Charlson index) [16].

### Patient selection

Adequate patient qualification and an appropriate choice of urinary diversion method is crucial in the prevention of complications after RC.

The American College of Surgeons recently activated an online surgical risk calculator that can quantify postsurgical risks and thus objectify decision-making. This tool is based on data from >1.4 million surgical cases indexed from approximately 400 medical centers that participate in the American College of Surgeons National Surgical Quality Improvement Program. Calculator can be found on <http://www.riskcalculator.facs.org> [18]. Furthermore, a nomogram has been developed to predict the likelihood of 90-day mortality among elderly patients. Authors

**Table 1.** The Clavien-Dindo Classification of surgical complications

Grade 1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade 2	Requiring pharmacological treatment with drugs other than such allowed for grade 1 complications. Blood transfusions and total parenteral nutrition are also included.
Grade 3	Requiring surgical, endoscopic or radiological intervention
Grade 3a	Intervention not under general anesthesia
Grade 3b	Intervention under general anesthesia
Grade 4	Life-threatening complications (including CNS complications)† requiring IC/ICU-management
Grade 4a	Single organ dysfunction (including dialysis)
Grade 4b	Multi-organ dysfunction
Grade 5	Death of a patient
Suffix 'd'	If the patients suffers from a complication at the time of discharge, the suffix 'd' (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

state that this tool, based on the experience of 220 patients aged greater than 75 years, has a 75% accuracy and may assist in the appropriate selection for RC [20]

It has been proven, that the higher age and the female gender statistically increased the risk of complications [19, 20]. Additionally, in patients older than 65 years, a lower preoperative Mini-Mental Status Examination score and an older age are significantly associated with the development of postcystectomy delirium [21]. However, during the qualification procedure, physiological, but not chronological age, should be taken into account. Wuethrich et al. analysed a group of 224 patients, over the age of 75, who had undergone RC. In the 35 patients an orthotopic intestinal reservoir was made, in 178 an ileal conduit and in only 11 a ureterocutaneousostomy. The total number of complications within 90 days after procedure was below 60%, which is comparable to the value of the RC complications in younger people. The oncological and functional results in the elderly were similar to those compared to the results in younger patients [22]. In another study presented by Tzortzis et al., authors presented a series of 18 RC in patients over 80 years old with an ASA (American Society of Anesthesiologists Physical Status Examination System) score of 3 or more, operated under combined regional anesthesia (spinal and epidural). The authors have obtained satisfactory results, a small amount of complications and no patient lost his life due to surgery [23]. Comploj et al. evaluated a large series of elderly ( $\geq 75$  years) patients undergoing radical cystectomy at four institutions. Comparing patients aged  $\geq 75$ –84 and  $\geq 85$  years did not reveal significant differences in complications, 30-day mortality, overall and cancer-specific survival rates. Only 90-day mortality rates were statistically higher in the  $\geq 85$ -year-old patients (13.5% vs. 32.3%) [24].

Obesity is the next factor that can be identified as an independent predictor of high-grade complications. Some authors state, that increased BMI independently poses a greater perioperative risk to the patient and contributes to the technical challenge of the cystectomy [20, 25]. Moreover, an obesity could also be associated with stomal complications after RC with ileal conduit [26].

Urinary diversion selection considers patient desire, surgeon preference, patient health status, disease severity and issues regarding cancer control, and targeted quality of life. Absolute contraindications for neobladder formation include impaired renal or/and hepatic function, physical or mental impairment, positive apical urethral margin and the unmotivated patient. Other factors such as bowel disease, ure-

thral pathology and a need for adjuvant chemotherapy may also be considered as contraindications.

Abe et al., presented an interesting study on a group of 668 patients comparing complications between RC with ileal conduit and neobladder in a 90 day follow-up. The authors retrospectively compared the results of both operations and showed that the overall number of complications between these two methods of urinary diversion did not differ statistically. In the group of neobladders there were more infections that occurred, whereas in the group of the ileal conduit there were more complications that occurred associated with wounds [27]. In the recent systematic review, authors found a higher rate of complications with the ileal conduit. Furthermore, high-grade complications were more common in ileal conduit cohorts [28]. However, what has to be kept in mind is that selection bias hinders credible comparison between the operative techniques. Ileal conduit surgery is commonly performed in patients with more advanced age, more advanced disease and more comorbidities which makes comparison difficult.

Patient comorbidity status can be analysed by various tools. One of the most commonly used is the ASA. It classifies the patients into six different groups starting with ASA I (healthy patient), and ending with ASA VI (brain-dead patient) [29].

Another popular tool, the Charlson Comorbidity Index (CCI), predicts mortality by basing on the presence of conditions like heart disease, AIDS, or various cancers. Each pathological disorder is assigned a score of 1, 2, 3, or 6, depending on the risk of associated mortality. Scores are summed to provide a total score to predict the total mortality [30]. Other systems like the frailty index, total psoas area (TPA) and The Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) with the Portsmouth predictor equation (P-POSSUM) can be also used to predict postoperative complications following RC [10, 31, 32].

It has been shown, that a higher ASA (e.g.,  $\geq 3$ ) or a higher CCI score (e.g.,  $\geq 3$ ) are associated with the postoperative complications development risk both within 30 and 90 days following the RC surgery [33, 34]. Other factors that should be taken into consideration is former pelvic/abdominal radiotherapy. Nevertheless, Nguyen et al. analysed 364 patients of who thirty-seven (10%) had a history of pelvic irradiation, and 327 (90%) that did not. Authors demonstrated that former radiotherapy, despite causing a more technically challenging operation, was not a predictor of survival length, BC recurrence or cancer specific mortality. There were no differences when comparing the rates of Grade 3 diversion-related complications (16% in irradiated and 13%

in nonirradiated patients). The rates of UE stricture (11% vs. 8%), pyelonephritis (14% vs. 13%), and urolithiasis (5% vs. 5%) throughout the course of the study did not differ statistically between patients with and without a history of pelvic irradiation [35].

### Centres and personnel

RC is a major surgery, which requires both medical and nursing staff experience. It has been shown, that in centres where RC is performed less frequently than 50/year, the complication rate is statistically higher than in centers where RC is performed routinely [36]. It has been demonstrated in another paper, that when compared with surgeons performing one RC annually, surgeons performing  $\geq 7$  RCs each year had 45% lower odds of major complications [37]. Likewise, significantly improved RC results are observed in residency teaching institutions and in large centers specializing in oncology compared with other centers [38]. Moreover, in the study published in *The Cancer Journal*, authors presented a relationship between the number of qualified medical personnel (licensed nurses or physiotherapists) and results of RC. It has been proven that there are fewer complications after RC when more staff takes care of the patients in the perioperative period [39].

### Fast-track/ERAS protocols

Another aspect in the complication reduction attempt concerns the protocols for patient preparation and management during and after RC. Recently, Fast-Track and ERAS (Enhanced Recovery After Surgery) protocols became popular and are widely used in gastrointestinal surgery [40]. Numerous good quality trials, conducted on patients undergoing bowel surgery proved that the compliance to the mentioned protocols allows for up to 50% reduction in the total amount of complications and for the significant shortening of hospital stays.

Both protocols are similar, yet, ERAS is much more complex. It involves intervention in all the phases of patient care.

It is clearly highlighted in the ERAS protocol, that the patient should be metabolically and nutritionally prepared for surgery [41]. A few days before the surgery, the patient receives an easily digestible diet, and the last meal is served in the evening before surgery. In addition, the evening before and in the morning of the surgery, the patient should intake carbohydrates containing fluids. It has been proven that the mentioned steps prevent increased catabolic processes, tissue insulin resistance and result in a faster return to normal functioning af-

ter surgery [42, 43]. Other authors also state, that the nutritional status measured by albumin levels is a predictor of RC survival [44]. Likewise, there is data to prove that oncological and surgical stress predisposes patients to immunoincompetency, with an increased risk of infectious complications. It is especially evident in malnourished patients [45]. A recent meta-analysis proved that enteral arginine-based pre- and postoperative nutritional supplementation is associated with a substantial reduction in infectious complications and hospital LoS [46].

In the mentioned protocols, it is not recommended to perform either mechanical or pharmacological bowel preparation. It has been shown that the 'purification' of the digestive tract does not reduce the amount of post-operative complications (enteric anastomotic leaks, intra-abdominal infections, wound complications) and is associated with patient discomfort, intestinal mucosa damage, dehydration, electrolyte disturbances and acid-base imbalance. It is permitted to perform a shallow enema [47, 48].

At day 0 after surgery, it is recommended to consume small amounts of fluids orally. At the first day liquid diet is employed, and light diet containing solid foods may be introduced at the second day after surgery. With this nutrition schedule, the right nitrogen compounds balance metabolism is maintained and the tissue insulin resistance is diminished. It has been proven that early enteral nutrition is not associated with a higher risk of bowel anastomosis leak/dehiscence, yet, is associated with an increased risk of nausea and vomiting, especially when opiates are used [49, 50, 51]. Postoperative total parenteral nutrition has been proved to be associated with a higher incidence of complications and infections [52]. For reducing nausea and vomiting, ERAS proposes avoiding patient overhydration, use of laxatives and prokinetic drugs, coffee consuming or chewing gum [53, 54, 55]. When comparing to nephrectomy and prostatectomy, RC has the highest risk for the venous thromboembolism (VTE) development. Thus, as for all oncologic and major pelvic surgeries, thromboprophylaxis with low molecular weight or unfragmented heparin, should be employed. Thromboprophylaxis should be used for up to 4–5 weeks after RC [56].

Additionally, compressive stockings and intermittent pneumatic compression devices can be used [40, 57]. Other strategies also concern mitigating of the delayed gastro-intestinal recovery which increases hospital LoS, morbidity and the total costs of care.

According to the Memorial Sloan Kettering Cancer Center (MSKCC) definition, postoperative ileus (POI) is a solid food intolerance at the 5<sup>th</sup> postoperative day with the need to hold oral nutrition because of bloating, nausea and vomiting and to establish

the gastric probe [13]. In order to reduce the POI incidence and length, careful opioid administration, wider non steroidal anti inflammatory drugs usage and placing of an epidural catheter are recommended. Additionally, Alvimopan administration is suggested. Alvimopan is a peripherally acting  $\mu$ -opioid receptor with limited ability to cross the blood-brain barrier, which therefore reduces many of the undesirable opioid side-effects without affecting analgesia. In a randomized trial, comparing RC patients receiving the Alvimopan and placebo demonstrated that compared to placebo, Alvimopan significantly reduced the POI and hospital length of stay. Alvimopan is suspected of provoking cardiovascular complications, yet, in this trial cardiovascular complications were even less frequent in the Alvimopan group [58]. These results were confirmed by recent meta-analysis [59].

Other contrivance implies readaptation of the peritoneum following lymphadenectomy. Roth et al. proved, that patients who have had readapted peritoneum had significantly less postoperative pain, POI time was shorter and had fewer complications in the early postoperative period when compared to the control group [60].

Also, interesting ideas for complication reduction during the intraoperative anesthesia are being published. What is likewise included in the ERAS protocol, during and after surgery, is that very restrictive fluid management should be introduced. It has been shown that both overhydration and fluid deficiency may impair bowel blood flow, increase rates of cardiopulmonary, wound, and anastomotic complications and in effect prolong POI [61, 62]. However, when compared to colorectal surgery, fluid monitoring in RC patients is more challenging, as urine output can be unreliable. Studer et al in his recent study proposed perioperative continuous norepinephrine administration in small dose (2  $\mu$ g/kg/h) combined with intraoperative restrictive hydration with Ring-

er's maleate solution. Less fluid was given during lymph node dissection and during cystectomy (the main period of bleeding), and more fluid was administered during construction of the urinary diversion. These modifications significantly reduced intraoperative blood loss, the rate of blood transfusions, the rate of gastro-intestinal complications and length of stay. Simultaneously, the authors did not observe an increased rate of infectious and cardiovascular complications, or tissue hypoperfusion [63, 64]. In the next Studer's paper, the authors demonstrated that patients undergoing RC with orthotopic neobladder, managed by the protocol described above, present much better daytime continence and improved erectile function in the one-year follow up when compared to patients in the control group [65].

## CONCLUSIONS

RC as a treatment free of complications, even in the hands of an experienced urologist, is very difficult to achieve. A large number of complications are acceptable in the name of good long-term results. Optimum results are possible with proper surgical technique, good patients and urinary diversion selection and proper patient management in pre-, peri, and postoperative period.

The presented research proves, that qualification for RC and the urinary diversion method should be based on objective morbidity rates (eg. CCI, ASA, cardiopulmonary reserve, hypertension) and not only on the patient's age [66, 67, 68]. It is highly recommended to adhere to fast-track/ERAS and anaesthesiological protocols. RC as a complicated and technically challenging procedure should be performed in centers with relevant surgical experience and with the appropriate amount of specialized personnel.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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