



Update on How to Improve the Outcome of Radical Cystectomy: A Systematic Review

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Abstract

Context Radical cystectomy (RCX) is the most difficult urologic procedure. It is usually performed in patients with morbidities and associated with a high rate of complications. So, every effort must be done to improve the outcome of this surgery.

Objective This systematic review tries to put an up to date analysis of the literature on how to improve the outcome of RCX.

Evidence acquisition A systematic literature search in the PubMed and Cochrane databases was performed from 1990 to July 2022 in English language using the keywords ‘radical cystectomy’, ‘Enhanced recovery’ and ‘Improved outcome’. Prospective studies were preferred; however, retrospective studies were used when no prospective studies were available.

Evidence synthesis In all, 237 relevant articles were identified and 46 articles were included in this systematic review. RCX may be associated by complications that may reach 70%. Preoperative patient preparation, optimization and counseling are critical. Enhanced recovery after surgery protocols should be adopted. The radicality of surgery is affected by the use of neo-adjuvant and/or adjuvant therapy, timing of surgery, the presence of a well-organized team and the surgeon experience. Ureteral dissection, urethral stump preparation and nerve sparing are three important steps during RCX greatly affecting the function of the following reconstructive step. Close follow up after RCX especially in the first two years is critical.

Conclusions Multiple factors should be followed to achieve good RCX. Regular skilled operative team, high volume surgeon, well equipped operative theater, excellent postoperative care are keys of success.

Key words Radical cystectomy, improved outcome, invasive bladder cancer

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Introduction

Bladder cancer (BCa) is one of the more common cancers in Egypt [1]. It is a lethal disease and any unplanned treatment may be fatal to the patient. RCX(Radical cystectomy) and UD(Urinary diversion) is the most difficult urologic procedure. It is usually performed in patients with morbidities and associated with a high rate of complications even in highly experienced centers [2]. The first chance in treating BCa is the only chance, as treatment of a recurrence is usually palliative. So, every effort must be done to improve the three outcomes after RCX which are the radicality, survival and function.

Multiple factors affecting these outcomes which includes; the patients' characteristics, tumor characteristics, previous management, type of RCX, and some technical points. The patients are usually elderly, hard workers in Egypt, having some co-morbid conditions as diabetes, hypertension, and cardio-pulmonary diseases. Some patients are delaying RCX wishing to preserve the bladder. The previous management- as bladder preservation, neo-adjuvant CTH(Chemotherapy), previous pelvic surgery- also are important factors. The different types of RCX, whether an early cystectomy, genital sparing, prostate/seminal sparing and salvage cystectomy, may have different outcomes. Some technical points as lymphadenectomy, urethral stump preparation, intestinal selection and the diversion type are also affecting the outcome (Table 1).

Herein, this systematic review tries to put an up to date analysis of the literature on how to improve the outcome of this kind of advanced surgery.

Evidence acquisition

A systematic review through the PubMed and Cochrane Library according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were performed [3]. The search included the period from 1990 to 2022, using the keywords 'radical cystectomy', 'Enhanced recovery' and 'Improved outcome'. The collected articles carefully examined and relevant data related to the proposed review were extracted by two authors. The search included studies related to the patient selection, preoperative preparation, intraoperative management, and postoperative care. Prospective studies were preferred; however, retrospective studies were used when no prospective studies were available. After applying these criteria, a total of 237 papers were identified. The authors then evaluated these articles based on study design, number of patients, and presence of relevant information in the study. Finally we identified 46 articles according to our search criteria that were included in our systematic review (Figure 1).

Results

In all, 237 relevant articles evaluating our research points were identified. Duplicate studies, case reports and abstracts were excluded. Only full-text articles in the English language were included. Of the 237 articles, 46 articles were included in our qualitative analysis based on our inclusion criteria. All articles were analyzed and divided into groups according to the question posed.

Discussion

RCX is a multistep surgery, and no single step is easy. Each step must be performed cautiously to avoid the high rate of its associated complications. We consider five important fundamentals that should be considered to improve the outcome: who is eligible and who is not, how to attain a good radical surgery, how to

achieve a smooth patient recovery, how to maintain and restore the functions after RCX and the importance of the availability of the patients for early detection and management of the complications.

Eligibility

RCX is indicated for the management of transitional cell carcinoma (T2-T4a, T1 tumors at high risk of progression i.e. high grade, multifocal, CIS and T1 patients failing intravesical therapy). Also, it is performed for aggressive variant as squamous cell carcinoma, adenocarcinoma and the micropapillary carcinoma of the bladder. It is contraindicated in patients with uncorrected cardiac, hepatic, renal or pulmonary diseases. Un-experienced surgeons, unequipped operative theater and inadequate postoperative care are also contraindications for this advanced surgery. So, this surgery is best mastered at high volume centers with high case load performing at least 40-50 RCXs/year [4].

Patients should be adequately counseled about the risks and benefits of this surgery and the quality of life changes after surgery. Also, the patient should be informed that the selected type of urinary diversion may be subjected to intraoperative conversion to another form due to any anatomic, oncologic or anesthetic necessities, although infrequent, is an option [2]. This realistic counseling greatly improve the patient's expectations.

Preoperatively, detailed history and physical examination should be performed. Imaging studies includes: abdominal ultrasound, enhanced abdomino-pelvic CT, chest x-ray ± chest CT, echocardiography and bone scan in certain patients. Laboratory workup as serum creatinine, complete liver functions, complete blood count and coagulation profile are basics. TUR biopsy from the bladder tumor and abnormal looking urothelium followed by examination under anesthesia then follows. For neobladder, TUR biopsy from prostatic urethra in males/bladder neck in females may be done [5].

Recoverability

In order to achieve a good recovery for this multistep surgery, some precautions, called enhanced recovery after surgery (ERAS), should be adopted. Preoperative medical optimization for any associated comorbid medical conditions should be done first. Bowel preparations can be safely omitted as the ileum is usually utilized for conduit and neobladder reconstruction. Clear fluids till 2 hrs and solid food till 6 hrs before the operation are safe. In order to the decrease the incidence of ileus, long-term sedatives and intravenous fluids overuse should be minimized. A recent randomized trial reported that the usage of intravenous lidocaine infusion with enhanced recovery pathway in patients underwent open RCX improve the gut motility [6]. Deep venous thrombosis (DVT) is not uncommon postoperative morbidity especially in elderly patients, females and after previous pelvic surgery. A well-fitting compressive stocking and low molecular weight heparin in the arms instead of thigh is a good prophylaxis [7]. Prophylactic antimicrobial 1 hr before skin incision and skin preparation with Chlorhexidine-alcohol are important to decrease wound infection. Epidural analgesia is better in relieving pain than opioids for the first 72 hrs. Perioperative fluid management and avoidance of intraoperative hypothermia are critical. Nasogastric tube is optional and not a routine [8]. Early oral diet as soon as the patients is passing flatus and early mobilization to improve the intestinal function and guard against DVT [2, 9].

Radicality

The most critical outcome is the radicality of surgery, which is affected by certain factors. These include, the use of neo-adjuvant

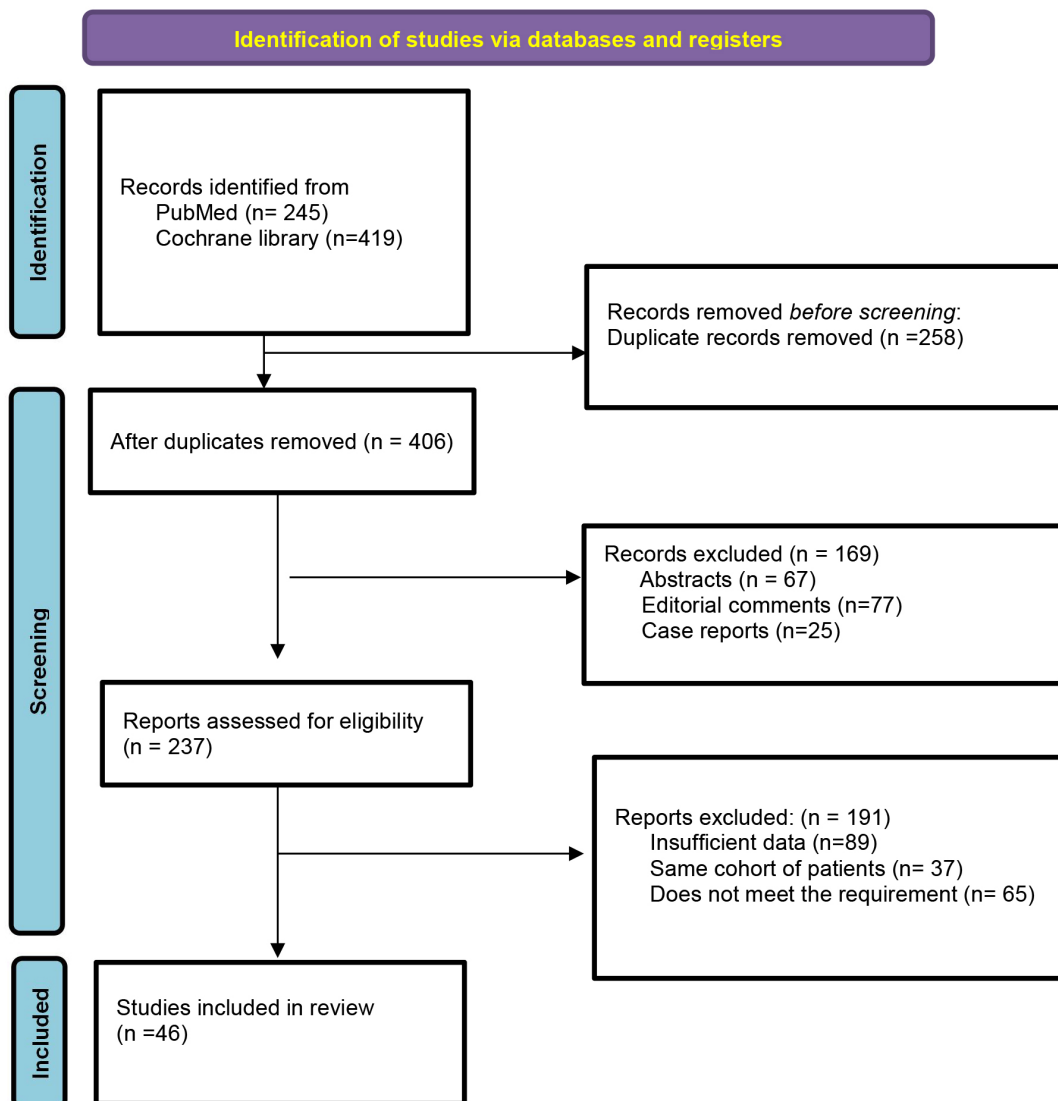


Figure 1. Flow chart for the selection of the studies according to the PRISMA statement.

and/or adjuvant therapy, timing of surgery, the presence of a well-organized team, some technical points and the surgeon impact.

Neo-adjuvant chemotherapy (NAC) is recommended for T2-T4 Bca. It is beneficial in early treatment of micrometastasis, assessing tumor response in vivo and delivery of the required dose of CTH before the occurrence of extensive fibrosis after surgery. It was shown to improve the survival by 5-8% [10]. However, a delay in RCX about 2 months and exposing some patients to CTH complications are considered limitations and reasons for being underutilized. The South West Oncology Group (SWOG) reported 5-year survival of 43% for the cystectomy group and 57% for the NAC plus surgery group. Also, another study showed 5% survival advantage with neoadjuvant cisplatin-based chemotherapy [11]. These data indicate that, 95% of patients receiving NAC may not benefit, its use is not a routine and needs judgment and is recommended in aggressive variants as micropapillary and small cell types [12].

Adjuvant chemotherapy is recommended for patients with advanced loco-regional disease if NAC was not utilized. It was

shown to improve the disease-free survival by 70% at 3 years in the chemotherapy group compared to 46% in the observation group [13]. On the other hand, neo-adjuvant radiotherapy is not recommended especially when RCX and urinary diversion is planned [14].

Timing of RCX is very crucial. A delay more than 3 months was shown to be associated with worse oncological outcomes [15-17]. Therefore, early cystectomy will improve the oncologic outcomes, survival and increase the possibility of having nerve sparing and orthotopic neobladder [18].

Regarding lymphadenectomy, all lymphatic tissues around the common iliac, external iliac, internal iliac, and the obturator group bilaterally should be removed. About 20 pelvic lymph nodes (LN) could represent the standard number of nodes removed. This enables clearance of 80% of positive nodes. Some advocates if frozen section reported no positive LN in the true pelvis, further cranial LN dissection of less importance. If the latter is not performed or identifies positive nodes, the inferior mesenteric artery should be the cranial limit of LN dissection [19-20]. A



Figure 2. Electro-thermal scissor.

study in which LN dissection was carried out up to the inferior mesenteric artery, showed that the prognosis of extrapelvic nodal disease is dismal. So, the usefulness of routine superextended LN dissection is questionable [21-22]. Moreover, to increase the yield of LNs, lymphatic tissues should be sent in separate submissions for pathologic evaluation [23].

The term “LN density” which is the ratio of the number of positive nodes to the total number of removed nodes may serve as a prognostic factor. It gives an idea about the extent of node dissection by the total number of nodes and the tumor burden by the number of positive nodes. A ratio of < 20% and 25% had been suggested to have better chance of survival than those with higher ratios [24-25]. However, absence of a fixed proximal extent of lymphadenectomy and standardization of the number of nodes that should be removed are limitations.

The main surgeon greatly affects the oncological outcome, the correct choice and performance of the reconstructive procedure. Also, the presence of a regular skilled operative team shortens

the duration of the operation [26]. Herr and colleagues concluded that the quality of RCX is more important than NAC. Also, It was shown that high volume urologists had a margin positive rate of 4% if compared to 14% of low volume ones. Local recurrence developed in 68% of margin positive patients if compared to 6% in margin negative patients. Mortality from RCX at low versus high volume hospitals was 3.1 % versus 0.7%. The overall survival is greatly affected by the surgical margins and the number of LN removed independent of patient age, pathological stage, nodal status and NAC and this is surgeon dependent [27].

Some technical points should be cautiously evaluated as prostatic capsule/seminal sparing and genital sparing RCX. The former initially performed to improve the potency by preserving the neurovascular bundle with a potency rate up to 90 %. But, the incidence of incidental prostatic carcinoma was high in cystoprostatectomy specimens (up to 48%). Moreover, it is associated with 10–15% higher oncological failure rate. So, it is considered by Hautmann a step in the wrong direction [28]. Genital sparing RCX was developed for a selected group of women especially young premenopausal female seeking childbearing [29]. Patients indicated should have an organ-confined disease located above the peritoneal reflection to avoid the oncological failure [30]. Additionally, preserving these organs provides a functional advantage after the orthotopic neobladder by providing a back support to avoid pouch-urethral angulation and chronic retention [10].

Regarding the instruments, in a prospective study evaluating the impact of vessel sealing devices on the outcome of open RCX in comparison with the conventional methods of dissection; RCX was carried out in conventional ligation/clip in a control group (n = 22) or electro-thermal device in the study group (n = 25). The latter was used to divide the posterior and lateral pedicles of bladder. They concluded that; the use of electro-thermal devices reduce the blood loss, saves the operating time and is useful in dividing deep vessels in the pelvis [31]. Additionally, in our practice we, use an electric scissor during lymphadenectomy, this shorten the duration of surgery to a great extent (**Figure 2**). We think that this saves the fitness of the surgeon for the 2nd step after RCX which is the urinary diversion. Also, long curved scissors of different lengths and curves to fit the different slopes of different prostates are important to preserve the maximal functional urethral length to overcome the difficulties of urethro-enteric anastomosis (**Figure 3**) [32].

The importance of minimally invasive laparoscopic and robotic



Figure 3. Surgical tray showing instruments of different lengths and curves.

Table 1. Factors affecting the outcome of radical cystectomy.

| Items | Characteristics |
|---------------------------|---|
| Patients | Medical morbidities Multiparty affect continence in females. Age affect continence in males Delaying cystectomy Heavy duty (farmers) Patients' motivation |
| Tumor characteristics | Type Stage Grade Number of recurrences |
| Previous management | Bladder preservation/duration/scheme Neoadjuvant CTH yes/No Previous pelvic surgery No/ type |
| Type of RCX | Timely cystectomy (RCX) Early cystectomy Fertility/ genital sparing RCX Prostate/seminal vesicle sparing RCX Salvage cystectomy Palliative cystectomy |
| Technical factors | Urethral stump Uretero-enteric anastomosis Lymphadenectomy Intestinal selection, isolation and anastomosis |
| Type of urinary diversion | UUC IC ONB CCUD |

RCX, Radical cystectomy; UUC, Uretero-ureterocutaneous; IC, Ileal conduit; ONB, Orthotopic neobladder; CCUD, Continent cutaneous urinary diversion.

RCX is addressed in multiple studies. These approaches assume fast recovery, less pain, blood loss and improved cosmosis [33]. However, the higher costs, the length of the procedure which is 2-4 hours more, lower number of retrieved lymph nodes, the unusual sites of metastatic disease that can be explained with hyper Co2 intra-peritoneal pressure and absence of long term results and randomized studies are their limitations [34].

Functionality

During RCX, some functions are lost; others are tried to be maintained and to be restored during urinary diversion. Ureteral dissection, urethral stump preparation and nerve sparing are three important steps during RCX greatly affecting the function of the following reconstructive step. Ureteric dissection should be in well vascularized a-traumatic manner, with no extensive upward dissection, as lengthy as possible, with safety margin, clipped if normal to allows hydro-distention and facilitates future re-implantation and preserve a dry field and limits the absorption through intestinal surface. The left ureter should have a smooth

curve if passing to the other side to be reimplanted in the future reservoir. The ureters should be spatulated and the uretero-enteric anastomosis should be stented and without tension. These precautions improve the uretero-enteric anastomosis and protect the upper urinary tract [32].

Nerve sparing surgery was shown not to improve the sexual function only, but improve the continence also as shown in multiple studies [35-37]. But, this should be done without negatively affecting the oncologic outcome [38].

The urethral stump should be dissected gently in a bloodless manner by careful securing the deep dorsal vein and the Santorini's plexus. Trying to preserve a maximal urethral length and preserving the NVB which will improve the continence also [37]. In our practice, at least six urethral sutures should be fixed to the urethral stump for good stabilization of the neobladder if it will be performed (**Figure 4**).

In female patients indicated for neobladder reconstruction, no dissection should be done anterior to the urethra along the pelvic floor. The endopelvic fascia should remain undisturbed. The posterior vaginal wall is opened below the cervix. In case

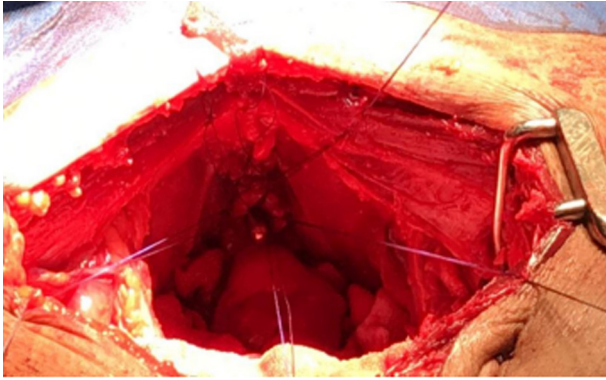


Figure 4. Well-prepared urethral stump with fixed urethral sutures.

of posterior bladder tumor, the anterior vaginal wall should be removed en bloc with the cystectomy specimen. In order to leave a functioning vagina, it should be closed horizontal or side to side and covered by omentum. The omentum serves as a barrier to prevent pouch-vaginal fistula [39]. Additionally, it serves as a back support behind the pouch to avoid the pouch falling back in the wide pelvic cavity and angulation of the poucho-urethral angle. The latter will lead to chronic retention [10].

Availability

Close follow up after RCX especially in the first two years is critical for three main endpoints; assessing the functional outcome, treatment of complications and for early detection and treatment of oncological failures.

RCX has significant peri- and postoperative complications rate up to 50–64 % [40-42]. The risk of postoperative complications and outcome are affected by several factors, such as performance status, age, preexisting comorbidities and surgeon experience [43-45]. Anyhow, the best functional and oncological results can be achieved if RCX and urinary diversion were performed in a high-volume hospital with at least 40–50 cases annually by high-volume surgeons and an experienced team [46].

To the best of our knowledge, to decrease the postoperative complications, a special attention should be paid to previously operated cases, previous radiotherapy, obese patients, elderly patients, previous bowel resection, ectopic pelvic kidneys, tumor inside diverticulum and transplanted kidney which are technically challenging and may be associated with a higher complication rate.

Conclusion

Proper patient selection, patient preparation, patient positioning, surgical exposure, meticulous lymphadenectomy, a-traumatic ureteric dissection, nerve sparing and urethral stump preparation are fundamentals of good RCX. Radiotherapy has no role before RCX. NAC is a standard, but it does not substitute for bad surgery. Regular skilled operative team, high volume surgeon, well equipped operative theater, excellent postoperative care are keys of success. Additionally, another way to improve your outcome is to “MEET THE EXPERTS”.

Author contributions

Ahmed M. Moeen is responsible on studies evaluation, selection, data collection and writing of the manuscript; Hassan A Aboul-Ella is responsible on studies evaluation, selection

and revision of the manuscript.

Competing interests

Dr. Ahmed M. Moeen declares that he has no conflict of interest.

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Ethical Approval

Ethical committee review was not required as the manuscript is a review of the published literature.

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