OPEN RADICAL CYSTECTOMY: SINGLE CENTER RESULTS AND OUTCOMES IN THE LAST FIVE YEARS

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SUMMARY – Radical cystectomy is a therapeutic modality of choice for many patients with muscle-invasive bladder cancer. We conducted a retrospective study of open radical cystectomies performed at a single Center from January 2017 to January 2022. Decision on the urinary diversion type was based on tumor stage, comorbidities, patient age, general condition and preferences. There were 19.5% of female and 80.5% of male patients, median age 67 (range 38-90) years. We performed 96 (44.7%) ureterocutaneostomies (UCS), 67 (31.2%) ileal conduit derivations, and 52 (24.2%) orthotopic neobladder derivations (OND). There were 17 (7.9%) complications after UCS, 7 (3.2%) after incontinent urinary diversion, and 7 (3.2%) after OND. Fifty-five (25.6%) patients developed early complications, of which 31 (14.4%) during the initial hospitalization period, and 24 (11.2%) required re-hospitalization in the 30-day postoperative period. The most common wound-related complication was wound dehiscence, most typically caused by infection. The main reason for readmission was urosepsis. The 30-day mortality rate was 0.9%. Late complications that occurred 30 days after the operation were found in 39 (18.1%) cases. Bladder cancer is a high-mortality disease that requires a multidisciplinary and personalized approach. Further development of multidisciplinary teams, perioperative and postoperative care, and follow-up strategy is needed to improve the oncologic and functional outcomes of this procedure.

Key words: Cystectomy; Urinary diversion; Bladder cancer; Ileal conduit; Survival

Introduction

Bladder cancer is the tenth most commonly detected tumor worldwide, and it is the sixth most common cancer in Croatia. It is a heterogeneous tumor that can be accompanied or associated with serious complications, leading to significant mortality and morbidity. The disease is three times more common in men¹. Approximately 25% of patients with bladder cancer were initially diagnosed with muscle-invasive bladder

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cancer (MIBC)². Due to its complex and aggressive biological behavior, the treatment of MIBC requires a multidisciplinary and multimodal approach.

The most common histologic subtype of MIBC is urothelial carcinoma (UC), in over 90% of cases, followed by UC with squamous or glandular differentiation, micropapillary UC, and others³. Oncologic outcomes depend on histology and clinical stage at the time of diagnosis, while also dictating the treatment strategy⁴.

Radical cystectomy is a globally accepted therapeutic method of treating patients with localized muscle-invasive, as well as non-muscle-invasive, high-risk bladder cancer^{5,6}. It is considered a major urologic sur-

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gery that involves several organ systems. Besides oncologic outcomes, emphasis is placed on preserving the quality of life after radical surgical treatment.

The objective of this paper is to report on surgical and oncologic outcomes of open radical cystectomy with various urine derivations regarding the postoperative histopathologic findings at our Center.

Material and Methods

We conducted a retrospective study of ORCs performed at a single Center from January 2017 to January 2022. Each patient scheduled for RC was discussed with a multidisciplinary team comprising of an urologist, oncologist, pathologist, and radiologist. The indications for RC were non-metastatic MIBC, immunotherapy and intravesical chemotherapy-refractory disease, and large tumors that are not suitable for endoscopic resection. The cystectomy procedure is carried out in the standard transperitoneal approach. In male patients, we performed cystoprostatectomy with pelvic lymph node dissection, and in female patients, we performed anterior exenteration of the pelvis with pelvic lymph node dissection. The decision on urinary diversion type is based on tumor stage, comorbidities, morphological and functional intestinal status, and patient age, general condition and preferences. Preoperative tumor staging is based on the thorax, abdomen and pelvis computed tomography scan. After discharge, patients were followed up with regular outpatient appointments depending on the final disease stage and urinary diversion type. Patients selected for neoadjuvant therapy (gemcitabine + cisplatin) had to be in good general condition, with no major comorbidities and with a lower Eastern Cooperative Oncology Group COG score. The need for adjuvant chemotherapy was discussed by the multidisciplinary team and administered by oncologists when indicated.

We analyzed demographic and perioperative data such as the type of urinary derivation, pathology report, TNM staging, neoadjuvant and adjuvant treatment. Complications were divided into two groups of early complications occurring in the first 30 postoperative days, and late complications occurring after 30 days and requiring patient readmission. Moreover, we analyzed tumor progression after RC, as well as overall survival. Patient medical histories were used for data collection, which was statistically analyzed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Released 2017; IBM Corp., Armonk, NY, USA).

Results

We performed 215 ORCs during the selected period. There were 19.5% of female and 80.5% of male patients, median age 67 (range 38-90) years. The types of urinary diversion are shown in Figure 1. We performed 96 (44.7%) ureterocutaneostomies (UCS), 67 (31.2%) ileal conduit derivations, and 52 (24.2%) orthotopic neobladder derivations (OND).

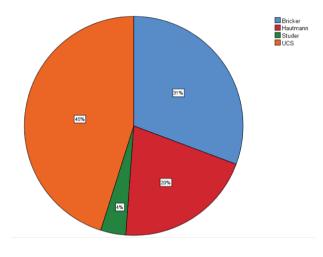


Fig. 1. Urinary diversion types. UCS = ureterocutaneostomy

The most common histopathologic finding was UC, which was found in 193 (89.8%) cases, while other types were diagnosed less frequently, as follows: squamous cell carcinoma in 9 (4.2%), adenocarcinoma in 6 (2.8%), neuroendocrine in 3 (1.4%) cases, and sarcomatoid bladder cancer in 1 (0.5%) case. TN stag-

Table 1. Tumor and node (TN) stages

T stage	Number (percentage)		
Т0	10 (4.7%)		
Ta	7 (3.3%)		
Tcis	10 (4.7%)		
T1	23 (10.7%)		
T2	49 (22.8%)		
T3	64 (29.8%)		
T4	44 (20.5%)		
N stage			
N0	126 (59.4%)		
N1	32 (15.1%)		
N2	46 (21.7%)		
N3	8 (3.8%)		

es are shown in Table 1. We performed 25 (11.6%) salvage cystectomies in patients with initial metastatic disease. Neoadjuvant chemotherapy was administered to 30 (13.9%) patients, while 79 (36.7%) patients received adjuvant oncologic treatment. Non-malignant cystectomies were performed in 3 (1.4%) cases, two in patients with cystitis cystica and one in a patient with a neurogenic bladder.

There were 17 (7.9%) complications after UCS, 7 (3.2%) after incontinent urinary diversion (IUD), and 7 (3.2%) after OND. Fifty-five (25.6%) patients developed early complications, of which 31 (14.4%) during the initial hospitalization period, and 24 (11.2%) required re-hospitalization in the 30-day postoperative period. These data are shown in Table 2. Wound dehiscences, most typically caused by infections, were the most common wound-related complications (Clavien-Dindo grade I-IIIb). Urinary complications were mostly related to intra-abdominal urine leakage and urinary infections (Clavien-Dindo grade IIIb). The main reason for readmission was urosepsis. Most cases of ileus were resolved with conservative therapy. In one case, bowel perforation occurred (Clavien-Dindo grade II-IIIb). Two patients developed deep vein thrombosis, one of them had pulmonary embolism. Pneumonia was the reason for prolonged hospitalization in four

Early complications	Number (percentage)	
Wound related complications	11 (21.2%)	
Urinary complications	22 (42.3%)	
Intestinal complications	10 (18.5%)	
Stoma related complications	1 (1.9%)	
Cardiopulmonary complications	4 (7.7%)	
Vascular complications	1 (1.9%)	
Neurologic complications	1 (1.9%)	
Patient death	2 (3.8%)	

Table	2.	Early	compl	ications

Table 3. Late complications

Late complications	Number (percentage)	
Wound related complications/	4 (10.3%)	
hernias		
Urinary complications	20 (51.3%)	
Stoma related complications	5 (12.8%)	
Anastomosis stenosis	7 (17.9%)	
Vascular complications	2 (5.1%)	

patients (Clavien-Dindo grade II). The 30-day mortality rate was 0.9%. Two patients died during initial hospitalization, one from surgical complications and the other one from myocardial infarction. Within 30 days of surgery, 24 patients were readmitted, of which 13 had UCS, 4 had IUD, and 7 had OND as urinary derivation.

Late complications that occurred 30-days after the operation were found in 39 (18.1%) cases, 17 patients had UCS, 9 had IUD, and 13 had OND. These data are shown in Table 3. Urinary complications were related to urinary infections, ureter-ileal anastomosis stenosis, and urinary incontinence after OND. Four patients were hospitalized due to hydronephrosis caused by ureteral-ileal anastomosis stenosis. There were 3 cases of parastomal hernias and one case of ventral hernia. One patient developed a vesicovaginal fistula.

The median follow up time was 11 (0-59) months and median overall survival 23 months (95% CI; 14.8-31.1). Kaplan-Meier curve of overall survival is shown in Figure 2a, and survival according to the choice of urinary diversion in Figure 2b. Progression to metastatic bladder cancer occurred in 33% of cases.

Discussion

Open radical cystectomy is one of the most demanding urologic operations, comprising of two steps, radical and reconstructive surgery. Classic radical cystectomy in men, besides removal of the urinary bladder, includes removal of the prostate, seminal vesicles, and pelvic lymph nodes. Due to anatomic differences, the procedure is different in women and includes extraction of the urinary bladder, anterior wall of the vagina, urethra, uterus, and lymph nodes.

When choosing a urine derivation, it is necessary to consider the quality of life, taking into account the oncologic segment of treatment and the expected overall survival rate. An important part of muscle-invasive bladder cancer treatment is the urinary diversion of choice, because most of the complications are diversion related⁷. Pre-existing comorbidities, age and frailty in combination with the choice of urinary diversion are important prognostic factors for complications and morbidity after radical cystectomy⁸. Age alone is not considered a criterion for offering continent diversion, but age >80 is considered the threshold for neobladder reconstruction⁹. Besides patient comorbidities, age and frailty score, several other clinical factors need to be considered when planning urinary diversion. The presence of N1 disease

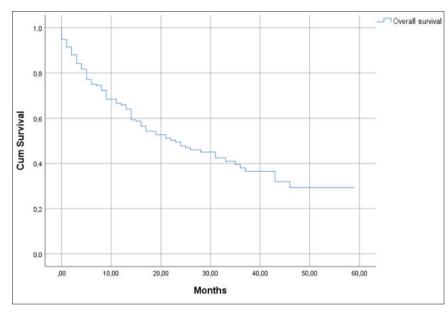


Fig. 2a. Kaplan-Meier curve of survival depending on urinary diversion.

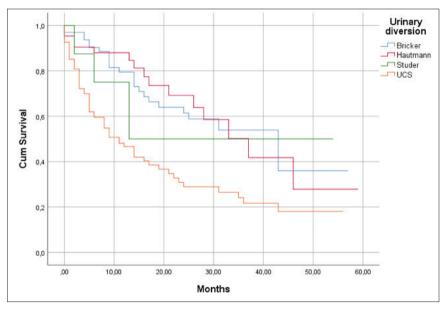


Fig. 2b. Kaplan-Meier curve of overall survival. UCS = ureterocutaneostomy

in the pelvis is not a contraindication for the neobladder, but N2 and N3 are¹⁰. If urethral infiltration is present, it could also be considered a contraindication for orthotopic neobladder derivation, but non-muscle-invasive bladder cancer of the urethra is not considered a contraindication¹¹. It is important to ensure that the patient is well informed about the risks, morbidities and impact on the quality of life when discussing the type of urinary diversion¹². All patients that are considered for radical cystectomy in our institution are presented to the multidisciplinary team of urologists, radiologists and oncologists. All the above criteria are considered, after which the decision on urinary derivation is made in compliance with the patients.

Ureterocutaneostomy is the simplest urinary diversion, usually reserved for frail patients with short

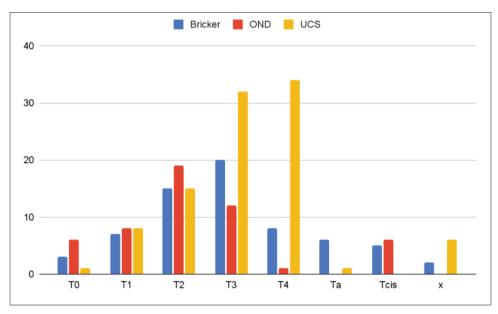


Fig. 3. Different derivations according to the stage of disease. OND = orthotopic neobladder derivation; UCS = ureterocutaneostomy; T = tumor stage

life expectancy. However, this derivation has the lowest complication rates in the short postoperative period, and the shortest intensive care unit and hospital stays^{13,14}. In the longer postoperative period, it has higher rates of UTI and ureteral stenosis than ileal diversions^{15,16}.

In our study, it was performed in 44.2% of patients. The median age of those patients was 72 (39-90) years. Other than age and frailty, another rationale in decision making was the clinical stage and intraoperative findings. This urinary diversion is usually reserved for patients with clinically advanced stage disease (T3b, T4), which is shown in Figure 3. Out of 108 patients with T3-T4 staged tumors, UCS was the choice of urinary diversion in 66 (61.1%) patients. The median survival time of these patients was 11 months (95% CI; 6.1-15.8).

Incontinent urinary diversion with the ileal conduit is another option, with good short-term outcomes and lower complication rates when compared to orthotopic neobladder derivation¹⁶. In our institution, it is usually reserved for patients with clinically higher stage disease, but are generally younger and in good health (Fig. 3). It was the choice of urinary diversion in 66 (30.7%) patients. The median age of these patients was 66 years.

Orthotopic neobladder derivation is a urinary diversion in which part of the selected bowel is used for neobladder formation, which is then connected to the urethra⁷. It was the urinary diversion of choice in 52 (24.2%) patients. It was usually reserved for younger patients with lower stage disease and those who were in generally good health (Fig. 3). The median age of these patients was 61 years.

Complications were reported in 22% of cases^{17,18}. The most common long-term complications were incontinence, ureter-intestinal stenosis, and metabolic disorders^{7,9,19}. Studies showed no differences in cancer-specific survival between patients with ileal conduit and neobladder diversion²⁰.

The largest number of derivations we performed in the five-year period were ureterocutaneostomias. The numbers of orthotopic and incontinent diversion were almost equal. As expected, we operated on four times more males than females.

The timing of RC is a very important prognostic factor for overall survival²¹. Studies showed that a delay by more than three months had a negative effect on overall survival²¹.

Neoadjuvant therapy, according to the GemCis protocol, was administered to patients who were fit enough for therapy. In one patient, progression to metastatic disease was observed while receiving therapy. It is important to note that, looking at the TNM stage, disease progression, and general condition of patients, approximately 50% of patients were not eligible for non-adjuvant therapy.

Studies showed that another important predictor of morbidity and mortality after radical cystectomy was the surgeon's and hospital's volume²²⁻²⁴. However, despite improvement in surgical techniques and use of enhanced postoperative recovery protocols, ORC remains one of the largest and most demanding surgical procedures performed by urologists²⁵. Major complications occur in approximately 5% and minor complications in 30% of cases^{5,6}. Our results revealed 31 (14.4%) patients with complications during hospitalization. The most common postoperative complications were wound dehiscence and infections. After discharge from the hospital and within 30 days of surgery, 24 (11.2%) patients were readmitted. Due to late complications of radical cystectomy (after 30 days), 39 (18.1%) patients were hospitalized during follow-up.

The most common histopathologic finding was urothelial carcinoma and the rarest was sarcomatous tumor. We had only one such case. Considering TNM classification, we mostly operated on T3 and T4 tumors. We had 49.1% of patients with positive lymph nodes, most of these N2 (Table 2). Some patients underwent salvage cystectomy, which explains the high proportion of UCs compared to other urine derivatives.

Postoperatively, the disease metastatically progressed in 71 (33%) patients during the follow-up period. In the follow-up period, until February 2022, 104 patients died.

According to data from the Central Health Information System of the Republic of Croatia (cro. CEZIH), 1231 radical cystectomies were performed in the reference interval. Our Center performed 17.47% of all procedures.

To our knowledge, there is only one similar publication of a large series of patients with bladder cancer that were treated surgically in Croatia, from the Rijeka University Hospital Center, published in 2010, and that publication is based on a similar research and number of patients but longer study period²⁶.

In conclusion, bladder cancer is a high-mortality disease that requires a multidisciplinary and personalized approach. In many cases, radical cystectomy is the modality of choice in treating these patients. Further development of multidisciplinary teams, perioperative and postoperative care, and follow-up strategy is needed to improve the oncologic and functional outcomes of this procedure.

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Sažetak

OTVORENA RADIKALNA CISTEKTOMIJA: REZULTATI I ISHODI JEDNOG CENTRA U POSLJEDNJIH PET GODINA

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Radikalna cistektomija je metoda izbora u liječenju bolesnika s mišićno invazivnim rakom mokraćnog mjehura. Provedena je retrospektivna studija otvorenih radikalnih cistektomija u KBC Zagreb od siječnja 2017. do siječnja 2022. godine. Odluka o derivaciji mokraće je temeljena na tumorskom stadiju, subolestima, dobi i općem stanju bolesnika te osobnim preferencijama. U studiji je bilo 19,5% žena i 80,5% muškaraca, njihov medijan dobi bio je 67 godina (raspon od 38 do 90 godina). Učinjeni su sljedeći zahvati: 96 (44,7%) ureterokutaneostomija, 67 (31,2%) derivacija s ilealnim konduitom i 52 (24,2%) ortotopične *neobladder* derivacije. Bilo je 17 (7,9%) bolesnika s komplikacijama nakon ureterokutaneostomije, 7 (3,2%) nakon derivacija s ilealnim konduitom i 7 (3,2%) nakon ortotopične *neobladder* derivacije. Rane komplikacije razvile su se kod 55 bolesnika od kojih 31 za vrijeme hospitalizacije, dok su preostalih 24 zahtijevale ponovnu hospitalizaciju kroz 30 dana poslije operacije. Dehiscencija rane bila je najčešća komplikacija, dok je najčešći razlog ponovne hospitalizacije bila urosepsa. Tridesetodnevna smrtnost bila je 0,9%. Kasne komplikacije koje su nastale nakon 30. poslijeoperacijskog dana zabilježene su u 39 bolesnika. Rak mokraćnog mjehura je visoko smrtonosna bolest koja zahtijeva multidisciplinski i personalizirani pristup. Potreban je daljnji razvitak multidisciplinarnosti, perioperacijske i poslijeoperacijske skrbi, kao i sveobuhvatnu skrb o bolesniku nakon hospitalizacije kako bi se postigli bolji onkološki i funkcionalni ishodi kod ovih bolesnika.

Ključne riječi: Cistektomija; Derivacija mokraće; Karcinom mjehura; Ilealni konduit; Preživljenje