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Morbidity and mortality after open radical cystectomy and ileal diversion – 10 years experience and a comprehensive assessment in a single tertiary center

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Open radical cystectomy (ORC) remains the gold standard for the treatment of muscle-invasive and high-risk non-muscle invasive bladder cancer unsuitable for bladder preservation techniques. Despite improvements in operative technique and perioperative care, it continues to be associated with significant complications. We analyzed our series of prospectively collected data of patients who underwent ORC at a tertiary referral academic center and evaluated early and late postoperative complications and mortality. The records of 391 ORCs with ileal diversion performed at our institution between January 2008 and July 2018 for non-metastatic transitional bladder carcinoma and other distinct pathological types were analyzed. Perioperative mortality was determined and 30-day and 90-day complications were reported according to the Martin Criteria and the European Association of Urology and graded according to the five-grade Clavien-Dindo classification. Univariate and multivariate analyses were used to evaluate predictors of complications and mortality. Gastrointestinal and infectious complications represented 41% and 43% of the total complications observed at 30 and 90 days after the surgery, respectively. The strongest predictor of infectious complications was the choice of ileal neobladder as the urinary diversion ($p \leq 0.0001$). Diabetes was a predictor of the overall, major and major infectious complications ($p<0.05$). The 30-day mortality rate was 1% while the 90-day mortality rate was 1.5%. Age ≥75 was the single predictor of mortality at both 30-days (p-value 0.003) and 90-days (p-value 0.01) in univariate and multivariate analyses. ORC is a morbid procedure, associated with a high mortality rate. Elderly patients should have proper counseling before the indication of this procedure. Gastrointestinal and infectious complications represent the most common and serious complications, and the study of their predictors is of the utmost importance.

Key words: bladder cancer, cystectomy, complications, morbidity, mortality

Despite the advances in cancer therapy, radical cystectomy (RC) and pelvic lymph node dissection remain the gold standard treatment in cases of muscle-invasive and high-grade non-muscle invasive cancer unresponsive to bladder-sparing strategies [1, 2]. It is so far the modality providing patients with the best oncological outcomes with a 5-year survival of 50% in cases of clinically localized invasive cancer [3], especially when combined with the use of neoadjuvant chemotherapy (NAC) that is proved to optimize overall survival (OS) in at least 5% [4–6].

Despite being the standard of care, open RC (ORC) is one of the most complex and extensive urological procedures. This is expressed by high rates of morbidity, mortality, reoperation rates as well as the length of hospital stay. The 3-month morbidity and mortality rates in the literature range from 19% to 64% [7] and from 0.8% to 8.3% [8, 9], respectively. Reoperation rates of 26.6% [10] and hospital stays in the range of 15–18 days are reported in the literature [11].

Recent advances in surgical technique and technology such as the use of electrothermal bipolar vessel sealing and mechanical devices and improvements in perioperative care with the adoption of protocols of enhanced recovery after surgery [12] have decreased intra-operative blood loss, need for transfusions, length of hospital stay (LOS), and complications [13, 14].

Further promising results have been obtained with minimally-invasive techniques such as the robotic-assisted approach which brings a decreased LOS and blood loss, with no significant difference regarding oncological outcomes [15] or the event of early and late perioperative complications [16]. However, this is an expensive approach reserved for centers equipped with a robotic system. Thus, ORC remains the most widely performed approach worldwide with shorter operation times [17], equivalent oncological and perioperative outcomes at substantially reduced costs [18].

We analyzed 30- and 90-day morbidity and mortality in a recent and homogenous series of patients indicated to ORC over a period of 10 years at our tertiary referral center using reporting methods described by Martin et al. [19] and the European Association of Urology (EAU) *ad hoc* panel [20] and the Clavien-Dindo classification of surgical complications [21]. We focused in particular on the study of major, infectious, and gastrointestinal complications and their predictive factors.

Patients and methods

We retrospectively reviewed the records of our prospectively collected database of patients consecutively operated at our institution from January 2008 to July 2018. All patients signed an informed consent with the collection of pre-, intra-, postoperative, and follow-up data and its analysis was approved by the ethics committee of the author's institution.

Indications for ORC were muscle-invasive disease, recurrent or high-risk tumors unresponsive to intravesical therapy, or non-muscle invasive tumors where complete endoscopic resection was not feasible. A total of 430 consecutive ORC were performed at our institution and the records of 391 patients with ileal diversion were analyzed. Patients treated for non-curative purposes (salvage or palliative cystectomy, cT4b), with a fast tumor progression within 90 days or a cause of death (accidental) unrelated to the performed surgery were excluded from this study (n=7) as well as patients treated with a different type (non-ileal) urinary diversion (n=32).

Our patient group consisted of 26% females and 74% males with a mean age of 65 ± 8.9 years (age interval between 21–85 years). The study population clinicopathological characteristics are shown in Table 1.

Preoperative assessment and patient preparation. Preoperative assessment included imaging studies (abdominopelvic CT scan and chest x-ray or thoracic CT scan), electrocardiography, echocardiography, spirometry, and routine blood samples. Bone scans were completed on an individual basis according to the physician's judgment. All patients received deep vein thrombosis (DVT) prophylaxis in the form of low-molecular-weight heparin applied one day before surgery continuing till the 30th postoperative day and compressive elastic stockings from the day of the surgery till full mobilization. Two days before the surgery patients were instructed to follow a low-residue diet, to drink a minimum of 2.5 liters including high-energy nutritional drinks. The day before surgery patients followed a liquid-only diet including high-energy supplements and received a sodium docusate and sorbitol-based enema as rectal preparation. Till February 2012, a mechanical bowel preparation was the standard of care, consisting of 4 liters of polyethylene glycol administered per os (64 g in one pack, total 4 packs).

Table 1. Clinical and pathological patient characteristics.

Parameter	N (%)
Gender	
Male	289 (74)
Female	102 (26)
Mean ± SD age (yrs)	65.0±8.9
Mean ± SD body mass index (kg/m^2)	27.4±4.6
Prior diabetes mellitus	86 (22)
Prior hypertension	238 (61)
Ischemic heart disease	47 (12)
Creatinine level μmol/l	
Up to 100	279 (72)
100-200	95 (24)
>200	9 (2)
N/A	8 (2)
ASA score	
N/A	4 (1)
I	43 (11)
II	218 (55.8)
III	124 (31.7)
IV	2 (0.5)
Age adjusted - Charlson comorbidity index	
0–1	37 (9.5)
2–3	129 (33)
4–5	129 (33)
6–7	82 (21)
8–10	14 (3.5)
Upper urinary tract obstruction	140 (36)
Non-muscle invasive bladder TCC	137 (35)
Lympho-vascular invasion	135 (35)
TNM primary tumor pathological stage	
pT0	51 (13)
CIS	22 (6)
pTa	15 (4)
pT1	51 (13)
pT2	63 (16)
pT3	105 (27)
pT4	84 (21)
Lymph node status	
pNx	16 (4)
pN0	279 (71)
pN+	96 (25)
Final histology	
No tumor at specimen	51 (13)
Urothelial TCC	318 (81)
Adenocarcinoma	10 (3)
Squamous cell carcinoma	4 (1)
Other	8 (2)
Previous surgery in abdomen or pelvis	180 (46)
Previous pelvic radiotherapy	19 (4.9)
Neoadjuvant chemotherapy	26 (6.6)
MVAC	3 (0.8)
Gemcitabine and cisplatin	20 (5)
Gemcitabine and carboplatin	3 (0.8)

This preparation was stopped in March 2012. Since February 2012, a bipolar electrocautery vascular sealing device was used in all surgeries. Before this, the approach to vasculature included vessel ligature, a monopolar coagulation device, and titanium clips. Antibiotic prophylaxis was started on the day of the surgery and the antibiotic of choice was amoxicillin and clavulanic acid or ampicillin and sulbactam. In cases of allergy to penicillin, cephalosporins, or a combination of fluoroquinolone and metronidazole was chosen. Antibiotics were standardly continued to postoperative day 5, but in some cases longer according to the patient's clinical condition. Twenty-six patients (6.6%) received preoperative neoadjuvant chemotherapy (NAC).

Surgical technique. Four experienced surgeons at our center performed all the procedures. In male patients, radical cystectomy included removal of the prostate, seminal vesicles, and distal ureters while in females the ovaries, uterus, adjacent vagina, and distal ureters were removed. Urethrectomy was performed in selected cases. Seventy-four cases (19%) were performed with an extraperitoneal approach, in which the peritoneum was preserved and fully closed.

Pelvic lymph node dissection (LND) included the external and internal iliac, obturator fossa, and common iliac nodes up to the crossing of the ureters. In selected cases, presacral and preaortic or precaval lymph nodes below the inferior mesenteric artery were also removed.

Urinary diversion types included ileal conduit (Bricker technique), orthotopic ileal neobladder (Studer or the Hautmann technique), and heterotopic neobladder.

The choice of urinary diversion depended on individual counseling, anatomical, oncological, and biological status of the individual.

Contraindications for orthotopic ileal neobladder included impaired renal or hepatic function, positive urethral margin, inability to perform clean intermittent catheterization, inadequate intellectual capacity or compliance, urinary stress incontinence, and severe intestinal diseases, as described by the EAU guidelines on muscle-invasive bladder cancer [2].

The types of urinary diversions performed, as well as surgical characteristics, hospital stay, 90-day events and mortality are listed in Table 2. No surgical staplers were used to suture the skin or create the urinary diversions and all diversions were hand-sutured. All uretero-intestinal anastomoses were stented for 10–12 days. All patients were monitored intra- and perioperatively by a central venous line and an arterial line and an epidural line was placed before the procedure for postoperative pain management. Patients did not standardly receive a nasogastric tube during the procedure, and this was only introduced in cases of early postoperative vomiting. Total parenteral nutrition was used in selected cases according to the general nutritional status and the occurrence of postoperative events delaying oral intake. Patients were standardly started on peroral fluids at postoperative day one and porridge at day two, according to individual tolerance and the presence of audible intestinal peristalsis.

Table 2. Surgical characteristics, hospital stay, 90-day events and mortality.

Parameter	N (%)
Urinary diversion	
Ileal conduit	287 (73.4)
Ileal neobladder	102 (26.1)
Other (heterotopic neobladder)	2 (0.5)
Surgical approach	
Intraperitoneal	317 (81.1)
Extraperitoneal	74 (18.9)
Operating time (min) mean ± SD	295±75
Blood loss (ml) mean ± SD	1,541±1,388
30-day transfusion units mean ± SD	3 ± 3.5
Length of hospital stay (days) mean ± SD	17 ± 10
Acute readmissions in 90 days	69 (17.6)
Reasons for readmissions at 90 days	
Fever of unknown origin, sepsis	31 (44.9)
Electrolyte dysbalance, metabolic acidosis	10 (14.5)
Nausea, vomiting	5 (7.2)
Abdominopelvic abscess	5 (7.2)
Pulmonary embolism	5 (7.2)
Deep vein thrombosis	4 (5.8)
Acute myocardial infarction	2 (3.0)
Paralytic ileus	2 (3.0)
Bowel occlusion	1 (1.4)
Dehiscence of ileal conduit	1 (1.4)
Lymphocele	1 (1.4)
Wound abscess	1 (1.4)
Reoperations in 90 days	49 (12.5)
Reasons for reoperation at 90 days	
Bowel occlusion	21 (42.9)
Pelvic hematoma	4 (8.2)
Pelvic abscess	4 (8.2)
Bleeding	4 (8.2)
Dehiscence of uretero-ileal anastomosis	4 (8.2)
Bowel leak	3 (6.1)
Rectal injury	2 (4.1)
Wound dehiscence	2 (4.1)
Dehiscence of ileal conduit	1 (2.0)
Dehiscence of neobladder	1 (2.0)
Dehiscence of uretero-neobladder anastomosis	1 (2.0)
Appendicitis	1 (2.0)
Clot retention in neobladder	1 (2.0)
Mortality	
30 day	4 (1)
90 day	6 (1.5)

In patients with orthotopic ileal neobladder, the urethral catheter was removed at postoperative day 14 without previous radiologic evaluation with retrograde contrast administration. In patients with ileal conduit, a urethral catheter was placed in the conduit and removed at postoperative day 7. Patients were hospitalized in intensive care during the first 24 hours until clinical stabilization and ventilation without an endotracheal tube and then transferred to a urology intermediate care unit for a median standard of 7 days.

All the patients were evaluated at our outpatient clinic within 30 days after discharge, with complete blood count, basic metabolic panel, and arterial blood gas examination. The majority of patients were followed at our outpatient clinic till postoperative day 90 or later, while the remaining minority was referred to their attending office urologist, who provided the clinical data relevant to the study.

Perioperative complications. Perioperative mortality was defined as death from a cause closely linked to the performed procedure within 30 and 90 days of surgery, while perioperative complications were defined as adverse events (AE) within 30 and 90 days of surgery. Complications were reported according to the Martin Criteria [19] and the standardized methodology proposed by the EAU guidelines [20] and graded according to the five-grade Clavien-Dindo system [21] and classified as 'minor' (grade 1–2) and 'major' (grade 3–5) as shown in Table 3.

A total of 474 postoperative complications occurred and were grouped into 11 categories: gastrointestinal, infectious, wound complications, bleeding, cardiac, genitourinary, pulmonary, thromboembolism, neurological, surgical, and miscellaneous.

To ensure uniformity and avoid interobserver variability, a single clinician was responsible for grading and assigning complications for the whole patient group. A second clinician was responsible for the validation of the result. None of them participated in the surgeries performed and thus were not procedure-biased.

Pathological staging was reported according to the 2002 TNM staging system [22] and tumor grading according to the World Health Organization 1973 classification [23]. The pathological stage was grouped as an organ-confined disease (pT0-2 pN0) and non-organ confined disease (pT3-4 or pN1-3).

The clinicopathological characteristics evaluated in the analysis were as follows: gender (M/F), age (≤74 and ≥75), body mass index (<25 kg/m^2, 25–30 kg/m^2 and >30 kg/m^2), diabetes (yes/no), hypertension (yes/no), ischemic heart disease (yes/no), creatinine level (≤100 μmol/l, 100–200 μmol/l and >200 μmol/l), preexisting hydronephrosis (unilateral, bilateral, absent), American Society of Anesthesiologists (ASA) score [24] (1–2 and 3–4), age-adjusted Charlson comorbidity index [25] (0–1, 2–3, 4–5, 6–7, and 8–10), pathologic stage (CIS, pT0-2 and pT3-T4), previous abdominal or pelvic surgery (yes/no), previous radiotherapy (yes/no), neoadjuvant chemotherapy (yes/no), urinary diversion type (ileal conduit and ileal neobladder), operating time (continuous variable), and estimated blood loss (continuous variable).

Statistical analysis. Continuous variables (estimated blood loss, operative time) were tested for normality (D'Agostino-Pearson test) and the test rejected normal distribution for both variables. Therefore, the estimated blood loss and operative time were analyzed as median with 95% confidence intervals (CI) of median, and the Mann-Whitney test was used for statistical evaluation. The body mass index (BMI), presence of hydronephrosis, Charlson comorbidity index, and preoperative creatinine level were categorized into more than two groups. Hence, the Chi-square test was used for the evaluation of such parameters. The categorical parameters with 2×2 values (e.g., gender; age group; prior diabetes) were compared using Fisher's exact test. A p-value <0.05 was considered to be statistically significant for all comparisons. The multivariate analysis was performed based on a logistic regression model with a stepwise selection model and a p-value <0.05 significance selection criterium of variables in the regression model. If there is no variable with p-value <0.05, the regression model cannot be fitted. The results of multivariate analysis are presented as odds ratio with 95% CI. Statistical analyses were performed in MedCalc Statistical Software version 19.1.5 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2020).

Results

After surgery, ten patients (2.6%) were immediately extubated and hospitalized in intermediate care, while 362 patients (93.0%) spent the first 24 hours in an intensive care unit and were then transferred to intermediate care for a median standard of 7 days. The remaining patients (4.6%) were, for various reasons, hospitalized for more than 24 hours in intensive care. The mean (SD) operative time was 295±75 minutes (range, 150–660 minutes) and the mean

Table 3. Overall complications at 30- and 90 days according to Clavien-Dindo classification.

Grade	Definition	N (%) complications (30 days)	N (%) complications (90 days)
0	No events observed under the general perioperative protocol described above	182 (46.5)	168 (43.0)
1	Oral medication or bedside intervention	93 (23.6)	116 (24.5)
2	Intravenous medication, prolonged total parenteral nutrition, blood transfusion (more than 4 units of packed red cells)	205 (52.0)	245 (51.7)
3	Interventional radiology, therapeutic endoscopy, intubation, angiography, reoperation	76 (19.3)	86 (18.1)
4	Life-threatening complication that required intensive care unit management or organ resection	16 (4.1)	21 (4.4)
5	Patient deaths	4 (1.0)	6 (1.5)

(SD) estimated blood loss was 1,541±1,388 ml (range, 200–1,800 ml). On average from January 2008 till February 2012, the estimated blood loss (EBL) was 2,295±2,162 ml (median 1,800 ml) and the average (SD) units of blood transfused postoperatively till 30 days was 5.4±4.6 units (median 4 units) versus the period starting in March 2012 till July 2018, when the mean (SD) EBL was 1,256±741 ml (median 1,000 ml) and the average (SD) units of blood transfused postoperatively till 30 days was 2.2±2.5 units (median 2 units). The p-value was <0.0001. A total of 280 patients (71.6%) received a minimum of 1 unit of packed red blood cells with a mean (SD) 3±3.5 units.

The overall mean (SD) length of hospitalization was 17±10 days (range 9–117 days). The mean (SD) postoperative hospital stay did not change significantly over time (p=0.68). From January 2008 till February 2012 the mean (SD) hospital stay was 18.5±13 days (median 15 days), while the mean (SD) hospital stay from March 2012 till July 2018 was 16.9±9 days (median 15 days). The hospital stay was significantly longer (p<0.0001) in patients with ileal neobladders (19.9±8.6; median 17 days) than in patients with ileal conduits (16.3±10.9; median 14 days) and the mean (SD) hospital stay of patients with any complication was higher than patients without complications (21.6±14.0 days vs. 13.6±2.5 days, p<0.0001). The overall readmission rate at 90 days was 17.6% and causes for readmission are shown in Table 2.

Four patients (1.0%) died within 30 days after surgery. One 79-year-old man died of intraoperative bleeding, one 84-year-old woman died due to respiratory insufficiency connected with pneumonia, and 2 patients (a 67-year-old and an 85-year-old man) died due to sepsis after an anastomotic bowel leak. At 90 days, 2 more patients died (1.5%), one 71-year-old woman died of sepsis and a 74-year-old man died of perforated peptic ulcer.

Overall, 32 intraoperative complications occurred in 391 patients. The most common were bleeding (n=23), obturator nerve injury (n=6), and rectal injury (n=3).

One-hundred and seven patients (27.4%) developed only one complication each at 30 days, 52 patients developed 2 complications at 30 days (13.3%) while 50 patients (12.8%) had three or more complications. During the postoperative course, 47 patients (12.0%) required reoperation within 30 days and 49 patients (12.5%) within 90 days due to a complication.

Report of the complications. A total of 394 complications were registered in 209 patients (53.5%) within 30 days of surgery.

Out of these, 141 patients (36.1%) had minor complications (grade 1–2), while 68 patients (17.4%) had a major complication (grade 3–5). At 90 days, 474 complications occurred in 223 patients (57.0%). Minor complications occurred in 146 patients (33.3%) and 77 patients (19.7%) had complications classified as major (grade 3–5) at 90 days.

An extended report of the 30-day and 90-day complications is shown in Table 4.

Table 4. Report of 30-day and 90-day complications in evaluated patients.

Category and type of complication	N (%) cases (30 days)	N (%) cases (90 days)
Gastrointestinal		
Paralytic Ileus	47 (12.0)	51 (13.0)
Bowel occlusion	21 (5.4)	22 (5.6)
Anastomotic bowel leak	3 (0.8)	3 (0.8)
Rectal injury	3 (0.8)	3 (0.8)
Acute cholecystitis	1 (0.25)	1 (0.25)
Acute pancreatitis	0 (0)	1 (0.25)
Diarrhea	2 (0.5)	3 (0.8)
Gastrointestinal bleeding	1 (0.25)	1 (0.25)
Rupture of peptic ulcer	0 (0)	1 (0.25)
Enterocutaneous fistula	1 (0.25)	2 (0.5)
Total	79 (20.2)	88 (22.5)
Infectious		
Fever without evident cause	49 (12.5)	70 (17.9)
Sepsis	21 (5.4)	29 (7.4)
Abdominal or pelvic abscess	6 (1.5)	8 (2)
Psoas muscle abscess	0 (0)	1 (0.25)
Gastroenteritis	3 (0.8)	3 (0.8)
Acute cholangitis	1 (0.25)	1 (0.25)
Acute epididymitis	1 (0.25)	2 (0.5)
Total	81 (20.7)	114 (29.2)
Bleeding		
Significant Bleeding	65 (16.6)	65 (16.6)
Cardiac		
Myocardial infarct	2 (0.5)	5 (1.3)
Arrhythmia	22 (5.6)	22 (5.6)
Hypertension	6 (1.5)	6 (1.5)
Total	30 (7.7)	33 (8.4)
Wound		
Dehiscence	16 (4.1)	17 (4.3)
Fasciitis	2 (0.5)	2 (0.5)
Abscess	5 (1.3)	6 (1.5)
Hematoma	4 (1.0)	4 (1.0)
Seroma	1 (0.25)	1 (0.25)
Total	28 (7.2)	30 (7.7)
Genitourinary		
Acute renal failure	3 (0.8)	7 (1.8)
Hydronephrosis requiring intervention	2 (0.5)	4 (1.0)
Clot retention	1 (0.25)	1 (0.25)
Dehiscence of neobladder	6 (1.5)	6 (1.5)
Dehiscence of ileal conduit	2 (0.5)	2 (0.5)
Dehiscence of uretro-ileal anastomosis	6 (1.5)	6 (1.5)
Dehiscence of uretro-neobladder anastomosis	1 (0.25)	1 (0.25)
Vagino-pelvic fistula	1 (0.25)	1 (0.25)
Neobladder-vaginal fistula	1 (0.25)	1 (0.25)
Stoma stenosis	1 (0.25)	1 (0.25)
Ureteral lesion	1 (0.25)	1 (0.25)
Urinary retention	0 (0)	3 (0.8)
Total	25 (6.4)	35 (9.0)

Table 4. Continued . . .

Category and type of complication	N (%) cases (30 days)	N (%) cases (90 days)
Pulmonary		
Pneumonia	6 (1.5)	7 (1.8)
Pneumothorax	6 (1.5)	6 (1.5)
Fluidothorax	3 (0.8)	4 (1.0)
Lung edema	4 (1.0)	4 (1.0)
Respiratory distress	5 (1.3)	5 (1.3)
Total	24 (6.1)	26 (6.6)
Thromboembolic		
DVT	4 (1.0)	6 (1.5)
Pulmonary embolism	2 (0.5)	6 (1.5)
Total	6 (1.5)	12 (3.1)
Neurological		
Delirium and/or agitation	9 (2.3)	9 (2.3)
Consciousness loss	2 (0.5)	2 (0.5)
Cerebrovascular accident	1 (0.25)	1 (0.25)
Adductor muscle deficit	6 (1.5)	6 (1.5)
Toxic encephalopathy	1 (0.25)	1 (0.25)
Total	19 (4.9)	19 (4.9)
Surgical		
Abdominal and/or pelvic hematoma	7 (1.8)	7 (1.8)
Lymphocele	4 (1.0)	4 (1.0)
Appendicitis	1 (0.25)	1 (0.25)
Neoblader-cutaneous fistula	0 (0)	1 (0.25)
Total	12 (3.1)	13 (3.3)
Miscellaneous		
Metabolic acidosis	6 (1.5)	15 (3.8)
Electrolyte disorder	4 (1.0)	6 (1.5)
Contact dermatitis	1 (0.25)	1 (0.25)
Conjunctivitis	1 (0.25)	1 (0.25)
Adverse reaction to blood derivatives	3 (0.7)	3 (0.7)
Adverse reaction to antibiotics	1 (0.25)	1 (0.25)
Depression	8 (2.0)	10 (2.5)
Elevation of liver enzymes	0 (0)	1 (0.25)
Hyperglycemia	1 (0.25)	1 (0.25)
Total	25 (6.4)	39 (10.0)

Prognostic factors predicting complications. Gastrointestinal (GIT) and infectious complications (major and minor) represented 41% and 43% of the total complications observed at 30 and 90 days from operation respectively. Tables 5 and 6 show the univariate and multivariate analyses for postoperative complications at 30 and 90 days of the whole patient cohort.

As gathered from Tables 5 and 6, the significant predictor of overall complications at 30 days (p=0.012) and 90 days (p=0.0005) was diabetes. A higher amount of blood loss was also a factor significantly correlated to 30-day and 90-day overall complications, while a longer operative time correlated to overall 30-day complications only.

Besides overall complications, diabetes was also a predictor of 30-day (p=0.038) and 90-day (p=0.008) high grade overall complications, infectious complications at 90 days (p=0.04), and high-grade infectious complications (p=0.02).

The choice ileal neobladder as the urinary diversion was the strongest factor correlating to the occurrence of infection at 30 days (p=0.0001) and 90 days (p<0.0001).

The sole predictor of gastrointestinal complications was the administration of neoadjuvant chemotherapy (p≤0.03).

Regarding mortality, age ≥75 years was the only predictor of mortality at both 30 and 90 days in univariate and multivariate analysis.

Previous comorbidities such as hypertension, ischemic heart disease, preoperative renal insufficiency, presence of hydronephrosis, and comorbidity classification systems such as the ASA score and the Charlson comorbidity index were not significant predictors of any complications or mortality.

Discussion

RC represents the best treatment option to date for patients with muscle-invasive and high-grade non-muscle invasive bladder cancer unresponsive or without indication for conservative therapy. It is one of the most complex procedures in urology, and despite constant advances in surgical technique, surgical instruments, anesthesiologic and perioperative care, it involves significant risk of short- and long-term complications. In the literature, 30-day morbidity rates of 26–64% and 90-day morbidity rates of around 64% [7] have been reported for ORC. Thirty-day mortality rates range between 0.3–4.5% [7, 8] and 90-day mortality rates range 2–7% [10] in previous studies. These figures are considered high for surgery with curative intent when compared to other cancers [26] and were shown to depend on a number of factors, including center volume, hospital characteristics, surgeon volume, and patient-related factors [27–29].

In our cohort, we observed 30-day and 90-day mortality rates of 1% and 1.5%, respectively. These numbers are lower than in most previously reported series [7, 8, 10, 11]. However, comparisons between different published series have to be done with caution since sample sizes, methodology, and homogeneities are diverse, especially when comparing cohorts with different median ages. As proven in our work, age is a strong predictive factor for both 30-day and 90-day mortality at univariate and multivariate analysis (p<0.03).

In our series, comorbidity scores such as ASA score or the age-adjusted Charlson comorbidity index failed to show any correlation to postoperative morbidity or mortality. These results are in line with some recently published studies [30].

While 3-month readmission rates as high as 27% have been reported [10], the readmission rate in our cohort was 17.6%, substantially less than reported. This could be related to a potential benefit of a longer initial postoperative hospital stay of our cohort (17±10 days).

Table 5. Univariate analysis of complications at 30-day and 90-day.

Parameter	30-day complications							90-day complications						
	Overall	High grade	Infectious	High Grade infectious	GIT	High grade GIT	Mortality	Overall	High grade	Infectious	High Grade infectious	GIT	High Grade GIT	Mortality
Gender Male/Female	0.42	1.0	0.26	0.75	0.25	0.83	1.0	0.25	1.0	0.18	0.58	0.21	1.0	0.65
Age (years) ≤74, ≥75	0.74	0.66	0.68	0.13	0.53	0.75	**0.003**	0.87	0.83	0.55	0.41	0.84	0.76	**0.01**
BMI category <25, 25-30, >30	0.99	**0.03**	0.85	0.54	0.3	0.11	0.48	0.67	**0.01**	0.54	0.91	0.21	0.07	0.33
Prior diabetes Yes/No	**0.03**	0.11	0.13	**0.04**	0.88	0.5	0.58	**0.003**	**0.04**	0.09	**0.03**	0.88	0.38	1.0
Prior hypertension Yes/No	0.6	0.41	0.44	1.0	0.51	0.84	0.65	0.3	0.9	0.47	1.0	0.53	0.71	0.68
Prior ischemic heart disease Yes/No	0.64	0.3	0.57	0.66	0.56	0.39	1.0	0.21	0.33	0.72	1.0	0.26	0.57	1.0
Creatinine level (μmol/l) <100, 100-200, >200	0.19	0.46	0.77	0.57	0.28	0.18	0.67	0.09	0.53	0.72	0.61	0.37	0.24	0.92
ASA score 1-2, 3-4	0.59	1.0	0.35	0.37	0.35	0.3	0.31	0.23	0.59	0.45	0.61	0.7	0.56	0.67
Age adjusted Charlson comorbidity index 0-1, 2-3, 4-5, 6-7, 8-10	0.84	0.93	0.5	0.47	0.32	0.92	0.63	0.51	0.69	0.7	0.51	0.34	0.95	0.4
Preoperative Hydronephrosis absent, unilateral, bilateral	0.57	0.78	0.28	0.91	0.44	0.71	0.62	0.66	0.58	0.81	0.78	0.31	0.7	0.75
TNM pathologic stage CIS, pT0, pTa, pT1, pT2/pT3, pT4	0.36	0.59	0.06	1.0	0.31	0.19	1.0	0.41	0.7	0.12	1.0	0.54	0.2	1.0
Previous surgery in abdomen/pelvis Yes/No	0.84	0.89	0.53	1.0	0.9	0.45	1.0	0.92	0.37	0.41	1.0	0.8	0.46	0.69
Previous radiotherapy Yes/No	0.16	0.55	0.39	1.0	**0.03**	0.38	1.0	0.09	0.39	0.27	1.0	0.39	0.39	1.0
Neoadjuvant chemotherapy Yes/No	0.23	0.28	0.8	1.0	**0.02**	0.71	1.0	0.42	0.44	0.81	1.0	**0.04**	0.71	1.0
Urinary diversion Ileal conduit/neobladder	0.64	0.88	**0.0002**	0.74	1.0	0.67	0.58	0.73	0.89	**0.00005**	1.0	1.0	0.83	0.35
Operating time (min)	**0.03**	0.73	0.07	0.06	0.42	0.69	0.87	0.08	0.84	0.11	0.07	0.2	0.86	0.56
Estimated blood loss (ml)	**<0.0001**	0.69	0.72	0.17	0.16	0.19	0.14	**<0.0001**	0.52	0.68	0.31	0.33	0.07	0.18

Note: Bold – significant p-value.

Table 6. Multivariate analysis of complications at 30-day and 90-day.

Outcome	Parameters	30-day analysis			90-day analysis		
		Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Overall complications	Diabetes	1.93	1.16–3.22	0.012	2.73	1.55–4.79	0.0005
	Estimated blood loss	1.00	1.0–1.0	<0.0001	1.0	1.0–1.0	<0.0001
	Preoperative creatinine 100–200 μmol/l	–	–	–	1.8	1.08–3.02	0.02
	Pelvic radiotherapy	–	–	–	0.34	0.12–0.96	0.04
High grade complications	Diabetes	1.9	1.04–3.48	0.038	2.2	1.23–3.92	0.008
Gastrointestinal complications	Neoadjuvant Chemotherapy	2.77	1.2–6.37	0.017	2.49	1.07–5.7	0.03
Infectious complications	Diabetes	–	–	–	1.77	1.02–3.08	0.04
	Urinary diversion Ileal Neobladder	2.75	1.64–4.6	0.0001	3.43	2.02–5.83	<0.0001
	Preoperative creatinine 100-200 μmol/l	–	–	–	1.8	1.02–3.16	0.04
High grade gastrointestinal complications	–	–	–	–	–	–	–
High grade infectious complications	Diabetes	4.2	1.28–13.8	0.02	3.34	1.25–8.94	0.02
	Operation time	1.0	1.0–1.01	0.036	–	–	–
Mortality	Age ≥75	22.4	2.04–246.6	0.01	7.39	1.26–43.46	0.027
	Estimated blood loss	–	–	–	1.0	1.0–1.0	0.044

In previous reports, reoperations within 30 days are commonly wound-related (wound dehiscence) with rates of 5.7% [11]. In our study, 47 patients (corresponding to 12% of the whole patient group) had a reoperation in the first 30 days. Most reoperations (42.9% of cases) were due to small bowel occlusion (SBO). This is possibly due to the fact that all anastomoses in our institution were hand sutured and this is considered to be more prone to SBO than the use of surgical staplers according to a meta-analysis with 5,084 patients [31] Previous recent ORC series have focused on the analysis of overall complications (minor and major) and complications specific to ileal conduits or neobladders. The individual study of gastrointestinal and infectious complications (accounting for 41% of overall and 46% of overall major complications at 30 days) and their predictive factors have not been analyzed by previous authors so far. In this work, we did a comprehensive analysis of these predictive factors.

Postoperative sepsis is a serious event with an adverse impact on postoperative mortality and mortality after hospital discharge [32]. We found that diabetes predicted the occurrence of both overall complications ($p<0.02$) and overall major complications ($p\leq0.038$) and high-grade infectious complications ($p=0.02$) at 30 and 90 days.

The strongest predictor of overall infectious complications at both 30 days (p-value 0.0001) and 90 days ($p<0.0001$) was the ileal neobladder as the urinary tract diversion, in line with previously published results [33].

Previous studies reporting on the effect of neoadjuvant chemotherapy (NAC) on short-term complications have concluded that there is no association with the occurrence of high grade and overall complications [34]. In our sample, we found a similar result concerning the administration of NAC and the occurrence of both high grade and overall complications, although a sub-analysis showed a correlation to overall gastrointestinal (GIT) complications at both 30 days ($p=0.017$) and 90 days ($p=0.03$).

There is conflicting evidence in the published series whereas previous pelvic radiotherapy does or does not influence morbidity after ORC. In our cohort, previous pelvic radiotherapy (pRT) weakly correlated with the less 90-day ($p=0.04$) overall complications. This is in clear contrast with the findings of Gontero et al. [35] in a recent retrospective multicenter study with a cohort of 682 patients, in which pRT correlated to a higher rate of major complications.

We take results concerning previous pRT and NAC administration in our sample with caution since the number of patients who received NAC or previous pRT was small (6.6% and 4.9% of the entire cohort respectively).

The introduction of a bipolar vessel sealer device (VSD) had a clear impact on EBL and transfusion units in our study. These were significantly less in the later period of the study. While there are few studies on the use of VSDs in ORC [36], this is in agreement with previously published studies on major abdominal and pelvic surgery [37].

Our study has some strengths. It includes both 30-day and 90-day data collected, reported and graded by a single clinician and validated by an independent clinician, using the same criteria over a period of 10 years. It includes a homogenous series of patients with similar demographics, from a delimited geographic area. A standardized surgical technique and perioperative protocol were applied and all surgeries were performed by four experienced urologists.

Although we tried to minimize biases, our study has drawbacks. It has the inherent weaknesses of a retrospective analysis of prospectively collected data of a single center with a relatively small cohort, resulting in the underpower of some results of the analysis and especially of the subgroup analysis.

ORC is a demanding surgical procedure associated with a high risk of postoperative complications and high mortality. Every center should adopt a standardized protocol and prospectively record their data to provide adequate counseling and improve the outcomes of their specific population.

We believe that a multicenter analysis with a well-defined standardized protocol including both 30-day and 90-day data with a focus on the predictors of gastrointestinal and infectious complications is urgently needed in order to overcome the previously mentioned drawbacks.

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