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Short-Term and Long-Term Morbidity after Radical Cystectomy in Patients with NMIBC and Comparison with MIBC: Identifying Risk Factors for Severe Short-Term Complications

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Cystectomy · Non-muscle-invasive bladder cancer · Complications · Morbidity · Bladder carcinoma · Urothelial neoplasm

Abstract
Introduction: RC represents a viable treatment option for certain NMIBC patients. However, studies investigating morbidity in the context of RC for NMIBC are scarce. The goal of the current study was to assess and compare morbidity after RC performed in patients with NMIBC and patients with MIBC and to identify risk factors for severe short-term complications. ***Methods:*** Medical records of 521 patients who underwent RC for bladder cancer were retrospectively reviewed. Patients were divided into patients with NMIBC and patients with MIBC. The groups were compared and risk factors for severe complications were identified. ***Results:*** RC for NMIBC was performed in 123 patients (23.6%). Histological upstaging was seen in 47 NMIBC patients (38.2%) and in 231 MIBC patients (58%, $p < 0.001$). OS was 29.8% and CSS was 15.5%. Both endpoints were higher for RC for MIBC ($p < 0.001$). More complications affecting the urinary diversion were seen with RC for NMIBC ($p = 0.033$) and more continent urinary diversions ($p = 0.040$) were performed in those patients. Obesity ($p = 0.008$), a higher ASA score ($p = 0.004$), and preoperative medical drug anticoagulation ($p = 0.025$) were risk factors for severe short-term morbidity after both, RC for NMIBC and for MIBC. ***Conclusion:*** Patients who underwent RC for NMIBC are exposed to a comparably high perioperative risk than patients with MIBC. RC seems to be a viable treatment option for certain NMIBC patients with a significant histological upstaging in both groups. In patients with obesity, a high ASA score, and with medical drug anticoagulation, the indication for surgery should be confirmed especially strict and possible treatment alternatives should be considered particularly thorough.

Introduction

While radical cystectomy (RC) has already been established as the golden standard therapy for patients with muscle-invasive bladder cancer (MIBC), it is also increasingly recognized as a viable treatment option for certain patients with non-muscle-invasive bladder cancer (NMIBC) [1–3]. In order to identify NMIBC patients,

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who are most likely to benefit from RC, patients can be subdivided into those with low-, intermediate-, high-, and very-high-risk for tumor progression according to the European Association of Urology Non-muscle-invasive Bladder Cancer Guideline Panel. The classification is based on tumor stage, grading, concomitant CIS, number of tumors, tumor size, and age [4]. Early RC is recommended in very-high-risk patients and also in certain high-risk patients, especially in case of BCG-unresponsive or BCG-relapsing tumors [3, 4].

Then again, RC is a potentially life-threatening, surgically challenging procedure. It usually involves bowel resection and construction of a urinary diversion after bladder removal, bearing a great risk for perioperative complications and even death with 90-day complication rates of up to 98% [5–9]. It is therefore essential to account for both potential benefits with improved oncological outcomes on the one hand and potential risks and (long-term) morbidity on the other hand, when counseling patients with (very)-high-risk NMIBC.

Studies reporting complication rates specifically after RC for NMIBC are scarce, and to the best of our knowledge, there is no study that identifies risk factors for severe short-term morbidity in the context of RC for NMIBC. However, since bladder-preserving treatment strategies constitute valid treatment alternatives in those patients, the indication for surgery must be confirmed especially strict and it is just the more important to evaluate, whether the known risk factors for severe complications after RC for MIBC account for NMIBC patients, as well. The aims of the current study were to (1) provide a comprehensive and thorough overview of (long-term) complications after RC for NMIBC at our institution, (2) compare patients and complication rates after RC for NMIBC and after RC for MIBC, and (3) identify risk factors that are associated with severe short-term morbidity.

Materials and Methods

Study Population

Medical records were screened retrospectively for patients who underwent an open RC for bladder cancer at our institution from 2008 to 2018. Only patients with histological evident urothelial carcinoma of the bladder including different histological subtypes from prior transurethral resection(s) of the bladder and without evidence of organ metastases in a preoperative computed tomography scan of chest, abdomen, and pelvis were included into the study. The study population was subdivided into patients who received RC for NMIBC and into those in whom RC was performed due to muscle-invasive disease (MIBC). Of 543 patients, who initially underwent RC for bladder cancer, 521 patients (95.9%) were included. Twenty patients were excluded because the reason for RC could not reliably be reconstructed from the available data or in case information was missing. Another 2 patients with NMIBC received neoadjuvant chemotherapy for a neuroendocrine subtype and neoadjuvant radio-chemotherapy, respectively, and were therefore also excluded. Surgery was conducted by 13 surgeons, 8 of whom were trained during the study period.

Data Acquisition

The electronical records at our institution were comprehensively reviewed in a retrospective manner. The electronical database comprised data on the inpatient stay, subsequent presentations via the emergency department or the outpatient clinic, and the uro-oncology ward. In addition to baseline characteristics (age, gender, body mass index [BMI]), preoperative variables (neoadjuvant chemotherapy, intravesical instillation therapy, prior transurethral resection(s) of the bladder, comorbidities, patient medication, clinical tumor staging), type of urinary diversion (ileal conduit, Indiana pouch [IP], ileal neobladder [NB], ureterocutaneostomy), and postoperative variables (time to patient discharge, time of intensive care unit [ICU] treatment, histopathological tumor staging) were assessed. We used an ERAS (enhanced recovery after surgery) protocol. The only change was the introduction of epidural analgesia in 2012, the rest of the protocol remained constant during the study period. The ERAS protocol is provided as a supplementary document. Comorbidities were recorded and the ASA score was applied [10]. The TNM-staging system was applied for histopathological tumor evaluation according to the criteria established by the UICC/AJCC for urothelial carcinoma [11].

Complication reporting was objectified according to a modified version of the Clavien Dindo Classification (CDC) and all complications were grouped depending on the site affected [12]. The CDC system divides complications from grade I to grade V depending on the severity of the complication or, more precisely, on the therapy or measurement necessary to treat a specific complication [12]. Complications were assessed and compared at different timepoints: (1) from postoperative days 0–30, (2) from postoperative days 31–90, (3) from postoperative months 4–12, and (4) from postoperative months 13–60.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics 28 (IBM, Armonk, NY, USA). An alpha value below 0.05 indicated statistical significance and all analyses were considered two-tailed. After testing for normal distribution, differences between patients who underwent RC for NMIBC and those with evidence of muscle-invasive disease were evaluated using χ^2 and Fisher's exact tests. Kruskal-Wallis and Mann-Whitney U tests were used for ordinal or nonnormally distributed variables. Statistical analysis also included regression analyses to identify risk factors for severe short-term morbidity after RC for NMIBC and RC for MIBC.

Results

Patient Characteristics

In the current study, the median age at surgery was 71 years (IQR 63–77) and 408 (78.3%) of the included participants were male. In 123 patients (23.6%), an RC

Table 1. Baseline patient characteristics

	Overall (n^a = 521)	NMIBC (n^a = 123)	MIBC (n^a = 398)	*p* value
Age, years, median (IQR)	71 (63–77)	70 (63–76)	71 (63–78)	0.327
Gender (male)	408 (78.3)	96 (78)	312 (78.4)	0.936
BMI, n^a (%)				0.347
<18.5	15 (2.9)	0 (0)	15 (3.8)	
18.5–24.9	165 (31.7)	41 (33.3)	124 (31.2)	
25–29.9	209 (40.1)	45 (36.6)	164 (41.2)	
>30	132 (25.3)	37 (30.1)	95 (23.9)	
ASA score, n^a (%)				0.584
1	21 (4.)	5 (4.1)	16 (4)	
2	219 (42)	55 (44.7)	164 (41.2)	
3	259 (49.7)	58 (47.2)	201 (50.5)	
4	20 (3.8)	5 (4.1)	15 (3.8)	
n.a.	2 (0.4)	0 (0)	2 (0.5)	
Urinary diversion, n^a (%)				0.040*
Ileal conduit	350 (67.2)	74 (60.2)	276 (69.3)	
Ureterocutaneostomy	19 (3.6)	5 (4.1)	14 (3.5)	
Ileal neobladder	119 (22.8)	31 (25.2)	88 (22.1)	
Indiana pouch	31 (6)	12 (9.8)	19 (4.8)	
Other	2 (0.4)	1 (0.8)	1 (0.3)	
T-stage last TUR-B, n^a (%)				<0.001*
≤pT1	127 (24.4)	123 (100)	4 (1.1)	
pT2	383 (73.5)	0 (0)	383 (96.2)	
*c*T3	5 (1)	0 (0)	5 (1.3)	
*c*T4	6 (1.2)	0 (0)	6 (1.5)	
Instillation therapy, n^a (%)	132 (25.3)	64 (52)	68 (17.1)	<0.001*
BCG	86 (16.5)	44 (35.8)	42 (10.6)	<0.001*
MMC/epirubicin/doxorubicin	64 (12.3)	30 (24.4)	34 (8.5)	<0.001*
Pathological T-stage at RC, n^a (%)				<0.001*
pT0/a/is/1	169 (32.4)	90 (73.2)	79 (19.9)	
pT2	84 (16.1)	12 (9.8)	72 (18.1)	
pT3	184 (35.3)	10 (8.1)	174 (43.7)	
pT4	84 (16.1)	11 (8.9)	73 (18.3)	
Pathological N-stage at RC, n^a (%)				<0.001*
pN0	350 (67.2)	103 (83.7)	247 (62.1)	
pN+	155 (29.8)	14 (11.4)	141 (35.4)	
pNx	16 (3.1)	6 (4.9)	10 (2.5)	
R-stage at RC, n^a (%)				0.042*
R0	452 (86.8)	114 (92.7)	338 (84.9)	
R+	60 (11.5)	8 (6.5)	52 (13.1)	
Rx	9 (1.7)	1 (0.8)	8 (2.0)	
Pathological LVI at RC, n^a (%)	184 (35.3)	17 (13.8)	167 (42)	<0.001*
Pathological VI at RC, n^a (%)	103 (19.8)	11 (8.9)	92 (23.1)	<0.001*
Multifocal tumor growth, n^a (%)	254 (48.8)	85 (69.1)	169 (42.5)	0.001*
Tumor size ≥3 cm, n^a (%)	304 (58.3)	49 (39.8)	255 (64.1)	<0.001*
Concomitant CIS, n^a (%)	157 (30.1)	36 (29.3)	121 (30.4)	0.186
Hospital stay, days, median (IQR)	17 (13–23)	17 (13–21)	17 (14–23)	0.404
ICU stay, days, median (IQR)	3 (2–5)	3 (2–4)	3 (2–5)	0.240
Neoadjuvant chemotherapy, n^a (%)	17 (3.3)	0 (0)	17 (4.3)	0.020*
Adjuvant chemotherapy, n^a (%)	55 (10.6)	7 (5.7)	48 (12.1)	0.023*
Recurrence-free survival (RFS), n^a (%)	400 (76.8)	109 (88.6)	291 (73.1)	<0.001*
RFS duration, months, median (IQR)	4 (0–17)	7 (0–32)	3 (0–12)	0.076
Overall mortality, n^a (%)	155 (29.8)	13 (10.6)	142 (35.7)	<0.001*
Cancer-specific mortality, n^a (%)	81 (15.5)	6 (4.9)	75 (18.8)	<0.001*
Follow-up of surviving patients, months, median (IQR)	4 (0–28)	8 (0–42)	4 (0–24)	0.156

Table 1 (continued)

	Overall (n^a = 521)	NMIBC (n^a = 123)	MIBC (n^a = 398)	*p* value
Drug anticoagulation and platelet antiaggregation therapy, n^a (%)	195 (37.4)	46 (37.4)	149 (37.4)	0.957
Preop. creatinine, mg/dL, median (IQR)	1.03 (0.84–1.3)	1.06 (0.83–1.21)	1.02 (0.85–1.33)	0.560
Preop. Hb, g/dL, median (IQR)	13.3 (11.7–14.6)	13.7 (12.5–14.7)	13.2 (11.5–14.5)	0.030*
Comorbidities, *n*/patient, median (IQR)	2 (1–3)	2 (1–4)	2 (1–3)	0.269
Comorbidity y/n, n^a (%)	416 (79.8)	102 (82.9)	314 (78.9)	0.330
Diabetes mellitus type II, n^a (%)	113 (21.7)	32 (26)	81 (20.4)	0.183
Cardiovascular disease, n^a (%)	340 (65.3)	89 (72.4)	251 (63.1)	0.059
Cardiac arrhythmias, n^a (%)	87 (16.7)	21 (17.1)	66 (16.6)	0.899
Thromboembolic disease, n^a (%)	34 (6.5)	8 (6.5)	26 (6.5)	0.991
Heart failure, n^a (%)	38 (7.3)	7 (5.7)	31 (7.8)	0.435
Pulmonary disorder, n^a (%)	67 (12.9)	17 (13.8)	50 (12.6)	0.716
Renal insufficiency, n^a (%)	59 (11.3)	13 (10.6)	46 (11.6)	0.763
Condition after organ transplant, n^a (%)	2 (0.4)	0 (0)	2 (0.5)	0.431
Condition post cancer disease, n^a (%)	95 (18.2)	29 (23.6)	66 (16.6)	0.079
Hematological malignancy, n^a (%)	13 (2.5)	5 (4.1)	8 (2)	0.202
Gastrointestinal disease, n^a (%)	13 (2.5)	1 (0.8)	12 (3)	0.172
Rheumatological disorder, n^a (%)	13 (2.5)	2 (1.6)	11 (2.8)	0.480
Neurological disease, n^a (%)	6 (1.2)	1 (0.8)	5 (1.3)	0.687

NMIBC, non-muscle-invasive bladder cancer; MIBC, muscle-invasive bladder cancer; IQR, interquartile range; BMI, body mass index; ICU, intensive care unit; TUR-B, transurethral resection of the bladder; BCG, Bacillus-Calmette-Guérin; MMC, mitomycin C; ASA, American Society of Anesthesiologists; RC, radical cystectomy. * Indicates statistical significance. [a] Numbers reflect the number of patients (percentages).

was performed for NMIBC. The overall mortality rate was 29.8% (155 patients) with a cancer-specific mortality of 15.5% (81 patients). The median follow-up period of patients, who did not die within the follow-up period, was 4 months (IQR 0–28). The relapse-free survival rate was 76.8% (400 patients). One hundred thirty-two patients (25.3%) received an intravesical instillation therapy (chemotherapy or BCG). Perioperative chemotherapy was conducted in 17 patients (neoadjuvant chemotherapy, 3.3%) and in 55 patients (adjuvant chemotherapy, 10.6%), respectively. An ileal conduit was performed in 350 patients (67.2%), ureterocutaneostomy in 19 patients (3.6%), an NB in 119 patients (22.8), and an IP in 31 patients (6%). NMIBC patients received more continent urinary diversions (p = 0.040). In 416 patients (79.8%), at least one comorbidity was present with cardiovascular diseases (65.3%), diabetes mellitus type II (21.7%), and cardiac arrhythmias (16.7%) being the most frequent ones. The median length of hospital stay was 17 days (IQR 13–23) and the median ICU-treatment duration was 3 days (IQR 2–5). The postoperative care was conducted according to an ERAS protocol (online suppl. document 1; for all online suppl. material, see www.karger.com/doi/10.1159/000528579). Further details including meticulous tumor-specific information are depicted in Table 1.

Differences between NMIBC and MIBC

There were no differences regarding patient age, gender, BMI, number and severity of comorbidities, or the inpatient-/ICU-treatment duration between NMIBC patients and MIBC patients. There were more continent urinary diversions (NB, IP) performed in NMIBC patients (p = 0.040). NMIBC patients showed higher Hb values (p = 0.030). Multifocal tumors were more frequently present in NMIBC-patients (p = 0.001). Higher pathological tumor stages (p < 0.001), higher rates of positive lymph nodes (p < 0.001), positive surgical margins (p = 0.042), venous-/lymphovascular infiltration (p < 0.001), and larger tumors were seen in MIBC patients (p < 0.001). Histological upstaging was seen in 47 NMIBC patients (38.2%) and in 231 MIBC patients (58%, p < 0.001). NMIBC patients showed higher RFS, CSS, and OS rates (all p < 0.001). Table 1 provides detailed information on patient and tumor characteristics comparing NMIBC patients with MIBC patients. Figure 1 represents a Kaplan-

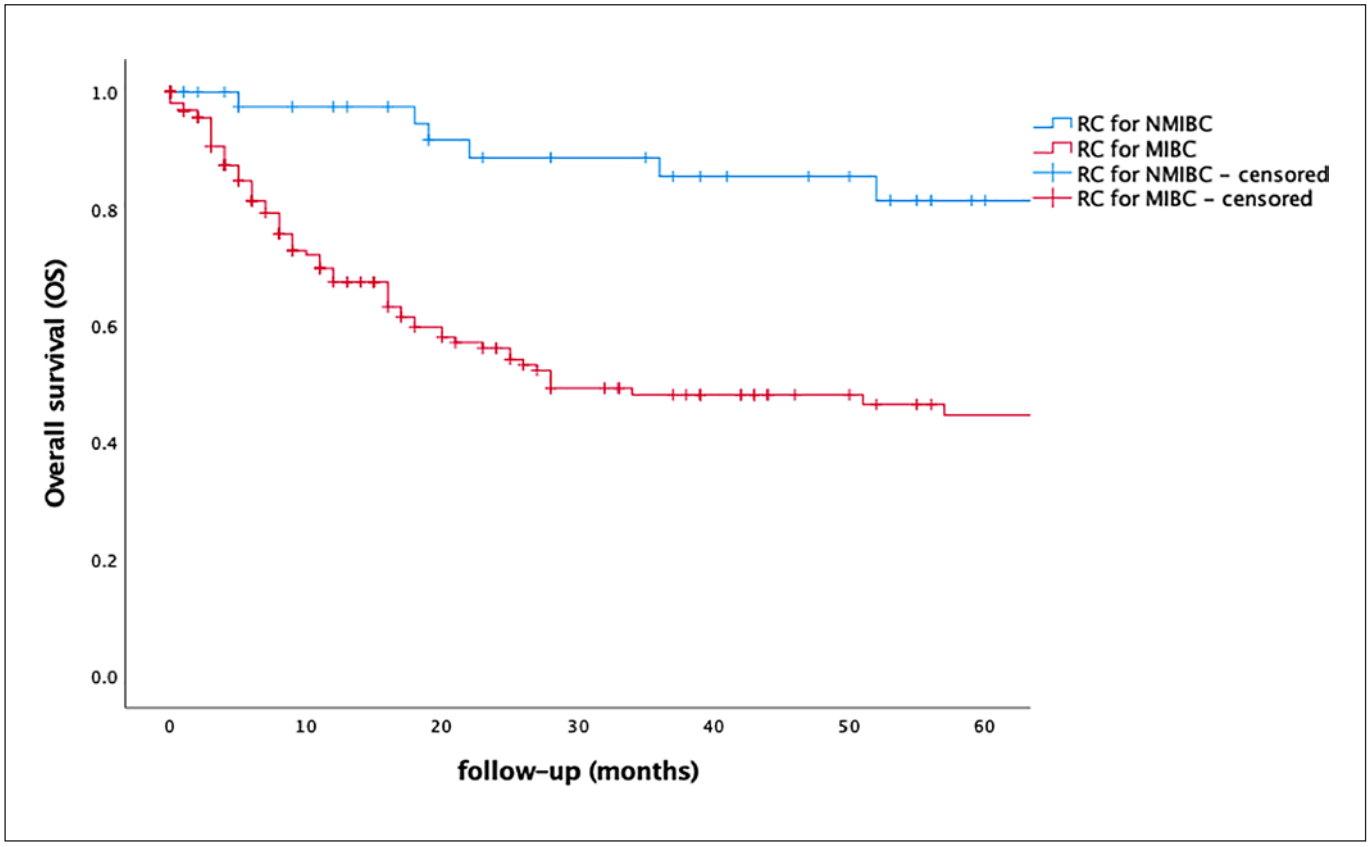

Fig. 1. Kaplan-Meier curves displaying overall survival after RC for NMIBC (blue line) and RC for MIBC (red line) over a time period of 5 years.

Meier curve comparing overall survival after RC for NMIBC and RC for MIBC.

Complications

In the early postoperative period, the most commonly observed complications (overall) were wound/skin complications (37.2%), bleeding complications (34.9%), and infectious complications (33.8%), which was true for RC for NMIBC and RC for MIBC. Compared to RC for NMIBC, we observed significantly higher rates of pneumonia (p = 0.042) and of bleeding complications (p = 0.041) with higher transfusion rates (p = 0.031), and higher rates of acute renal insufficiency (p = 0.016) in patients, who underwent RC for MIBC (Table 2).

From 1 to 3 months, we found significantly more complications affecting the urinary diversion (p = 0.033) with higher rates of urethral strictures (p = 0.049) and a higher amount of urinary diversion complications per patient (p = 0.006) in NMIBC patients compared to MIBC patients (online suppl. Table 1). The rate of metabolic complications due to absorption disorders was also higher with RC for NMIBC (p = 0.018). Online supplementary Tables 1–3 provide detailed information on the observed complications after RC for NMIBC and after RC for MIBC with regard to different timepoints postsurgery.

Risk Factors for Developing a Severe Complication (≥CDC IIIb) within 30 Days Postsurgery

Preoperative medical anticoagulation (p_1), higher ASA scores (p_2), and obesity (p_3) were identified as risk factors for severe short-term morbidity after both RC for NMIBC (p_1 = 0.025, p_2 = 0.004, p_3 = 0.008) and RC for MIBC (p_1 < 0.001, p_2 < 0.001, p_3 = 0.001). A higher age at surgery was associated with severe complications after RC for MIBC (p = 0.004), but not after RC for NMIBC (p = 0.302). Further details are depicted in Table 3.

Table 2. Observed complications within 30 days postsurgery with regard to the affected organ system

Complication	Overall, *n*[a] (%)	NMIBC, *n*[a] (%)	MIBC, *n*[a] (%)	*p* value
Cardiological complications				
Cardiological complications y/n, *n*[a] (%)	45 (8.6)	7 (5.7)	38 (9.5)	0.170
Amount, *n*/patient, median (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	1.000
Myocardial infarction, *n*[a] (%)	5 (1)	1 (0.8)	4 (1)	1.000
Syncopation, *n*[a] (%)	5 (1)	0 (0)	5 (1.3)	0.598
Cardiac arrhythmia, *n*[a] (%)	35 (6.7)	6 (4.9)	29 (7.3)	0.332
Thromboembolic complications				
Thromboembolic complication y/n, *n*[a] (%)	11 (2.1)	0 (0)	11 (2.8)	0.074
Amount, *n*/patient, median (IQR)	1 (1–1)	0 (0–0)	1 (1–1)	n.a.
Pulmonary embolism, *n*[a] (%)	7 (1.3)	0 (0)	7 (1.8)	0.206
Thrombosis, *n*[a] (%)	4 (0.8)	0 (0)	4 (1)	0.577
Pulmonary complications				
Pulmonary complications y/n, *n*[a] (%)	82 (15.7)	13 (10.6)	69 (17.3)	0.063
Amount, *n*/patient, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	0.362
Pneumonia, *n*[a] (%)	44 (8.4)	5 (4.1)	39 (9.8)	0.042*
Respiratory insufficiency, *n*[a] (%)	66 (12.7)	11 (8.9)	55 (13.8)	0.140
Bleeding complications				
Bleeding complications y/n, *n*[a] (%)	182 (34.9)	34 (27.6)	148 (37.2)	0.041*
Amount, *n*/patient, median (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	0.913
Secondary bleeding, *n*[a] (%)	12 (2.3)	3 (2.4)	9 (2.3)	1.000
Postoperative transfusion, *n*[a] (%)	180 (34.5)	33 (26.8)	147 (36.9)	0.031*
Neurological complications				
Neurological complication y/n, *n*[a] (%)	49 (9.4)	8 (6.5)	41 (10.3)	0.208
Amount, *n*/patient, median (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	0.407
Apoplex, *n*[a] (%)	6 (1.2)	0 (0)	6 (1.5)	0.344
Nerve lesion, *n*[a] (%)	5 (1)	0 (0)	5 (1.3)	0.598
Delirium, *n*[a] (%)	38 (7.3)	8 (6.5)	30 (7.5)	0.700
Seizure, *n*[a] (%)	3 (0.6)	0 (0)	3 (0.8)	1.000
Gastrointestinal complications				
Gastrointestinal complications y/n, *n*[a] (%)	76 (14.6)	18 (14.6)	58 (14.6)	0.962
Amount, *n*/patient, median (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	0.676
Bowel obstruction/ileus, *n*[a] (%)	71 (13.6)	17 (13.8)	54 (13.6)	0.993
Intestinal ischemia/perforation, *n*[a] (%)	3 (0.6)	0 (0)	3 (0.8)	1.000
Enterovaginal fistula, *n*[a] (%)	3 (0.6)	1 (0.8)	2 (0.5)	0.560
Urologenital complications				
Urogenital complications y/n, *n*[a] (%)	86 (16.5)	14 (11.4)	72 (18.1)	0.070
Amount, *n*/patient, median (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	0.826
Acute renal insufficiency, *n*[a] (%)	44 (8.4)	4 (3.3)	40 (10.1)	0.016*
Hydronephrosis, *n*[a] (%)	36 (6.9)	8 (6.5)	28 (7)	0.807
Stress incontinence, *n*[a] (%)	3 (0.6)	1 (0.8)	2 (0.5)	0.560
Urinoma, *n*[a] (%)	11 (2.1)	2 (1.6)	9 (2.3)	1.000
Fistula neobladder, *n*[a] (%)	3 (0.6)	0 (0)	3 (0.8)	1.000
Ureteral stenosis, *n*[a] (%)	2 (0.4)	1 (0.8)	1 (0.3)	0.421
Wound/skin complications				
Wound/skin complication y/n, *n*[a] (%)	194 (37.2)	46 (37.4)	148 (37.2)	0.938
Amount, *n*/patient, median (IQR)	2 (1–2)	2 (1–2)	2 (1–2)	0.241
Skin dehiscence, *n*[a] (%)	96 (18.4)	24 (19.5)	72 (18.1)	0.780
Ureteroenteric anastomotic leak, *n*[a] (%)	67 (12.9)	19 (15.4)	48 (12.1)	0.360
Disturbance of wound healing, *n*[a] (%)	136 (26.1)	31 (25.2)	105 (26.4)	0.725
Fascial dehiscence, *n*[a] (%)	34 (6.5)	11 (8.9)	23 (5.8)	0.232
Infectious complications				
Infectious complications y/n, *n*[a] (%)	176 (33.8)	35 (28.5)	141 (35.4)	0.153
Amount, *n*/patient, median (IQR)	1 (1–3)	1 (1–2)	1 (1–3)	0.353
Urinary tract infection, *n*[a] (%)	95 (18.2)	22 (17.9)	73 (18.3)	0.909
Pyonephrosis, *n*[a] (%)	12 (2.3)	1 (0.8)	11 (2.8)	0.310
Urosepsis, *n*[a] (%)	8 (1.5)	1 (0.8)	7 (1.8)	0.687

Table 2 (continued)

Complication	Overall, *n*[a] (%)	NMIBC, *n*[a] (%)	MIBC, *n*[a] (%)	*p* value
Wound infection, *n*[a] (%)	24 (4.6)	5 (4)	19 (4.8)	0.718
Abscess, *n*[a] (%)	16 (3.1)	1 (0.8)	15 (3.8)	0.135
Peritonitis, *n*[a] (%)	33 (6.3)	5 (4.1)	28 (7)	0.223
SIRS/sepsis, *n*[a] (%)	74 (14.2)	13 (10.6)	61 (15.3)	0.168
Gastrointestinal infection, *n*[a] (%)	11 (2.1)	3 (2.4)	8 (2)	0.729
Cholecystitis, *n*[a] (%)	1 (0.2)	0 (0)	1 (0.3)	1.000
Central venous catheter infection, *n*[a] (%)	2 (0.4)	1 (0.8)	1 (0.3)	0.421
Other infections, *n*[a] (%)	5 (1)	3 (2.4)	2 (0.5)	0.091
Other complications				
Other complications y/n, *n*[a] (%)	74 (14.2)	18 (14.6)	56 (14.1)	0.671
Amount, *n*/patient, median (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	0.333
Lymphocele/lymphedema, *n*[a] (%)	37 (7.1)	11 (8.9)	26 (6.5)	0.388
Allergical reaction, *n*[a] (%)	4 (0.8)	1 (0.8)	3 (0.8)	1.000
Liver failure, *n*[a] (%)	3 (0.6)	0 (0)	3 (0.8)	1.000
Metabolic acidosis, *n*[a] (%)	30 (5.8)	6 (4.9)	24 (6)	0.606
Complications affecting the urinary diversion				
Complications affecting the urinary diversion, *n*[a] (%)	14 (2.7)	5 (4.1)	9 (2.3)	0.339
Amount, *n*/patient, median (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	1.000
Parastomal hernia, *n*[a] (%)	5 (1)	3 (2.4)	2 (0.5)	0.091
Ureteroenteric anastomotic stenosis, *n*[a] (%)	2 (0.4)	0 (0)	2 (0.5)	1.000
Neobladder leakage, *n*[a] (%)	2 (0.4)	1 (0.8)	1 (0.3)	0.421
Conduit stenosis, *n*[a] (%)	1 (0.2)	1 (0.8)	0 (0)	0.239
Conduit necrosis, *n*[a] (%)	4 (0.8)	0 (0)	4 (1)	0.577
Highest complication according to CDC				0.558
CDC grade I, *n*[a] (%)	33 (6.3)	11 (8.9)	22 (5.5)	
CDC grade II, *n*[a] (%)	138 (26.5)	31 (25.2)	107 (26.9)	
CDC grade IIIa, *n*[a] (%)	8 (1.5)	3 (2.4)	5 (1.3)	
CDC grade IIIb, *n*[a] (%)	121 (23.2)	31 (25.2)	90 (22.6)	
CDC grade IVa, *n*[a] (%)	32 (6.1)	6 (4.9)	26 (6.5)	
CDC grade IVb, *n*[a] (%)	14 (2.7)	4 (3.3)	10 (2.5)	
CDC grade V, *n*[a] (%)	28 (5.4)	2 (1.6)	26 (6.5)	
Complication y/n, *n*[a] (%)	374 (71.8)	88 (71.5)	286 (71.9)	0.829
Total number of complications, *n*/patient, median (IQR)	2 (0–4)	1 (0–3)	2 (0–4)	0.196
Revision surgery				
Revision surgery y/n, *n*[a] (%)	171 (32.8)	41 (33.3)	130 (32.7)	0.977
Amount, *n*/patient, median (IQR)	2 (1–4)	2 (1–3)	2 (1–4)	0.483
Wound healing disturbances, *n*[a] (%)	120 (23)	27 (22)	93 (23.4)	0.682
Hematoma/urinoma/lymphocele/abscess, *n*[a] (%)	31 (6)	6 (4.9)	25 (6.3)	0.541
Nephrostomy/ureteral stent, *n*[a] (%)	27 (5.2)	6 (4.9)	21 (5.3)	0.834
Urinary diversion, *n*[a] (%)	20 (3.8)	4 (3.3)	16 (4)	0.795
Enteral anastomosis, *n*[a] (%)	20 (3.8)	5 (4.1)	15 (3.8)	1.000
Other reasons, *n*[a] (%)	7 (1.3)	2 (1.6)	5 (1.3)	0.674
Erythrocyte transfusion				
Overall transfusion y/n, *n*[a] (%)	296 (56.8)	62 (50.4)	234 (58.8)	0.070
Amount, *n*/patient, median (IQR)	2 (2–4)	2 (2–4)	2.5 (2–4)	0.623
Preoperative transfusion y/n, *n*[a] (%)	25 (4.8)	3 (2.4)	22 (5.5)	0.153
Preoperative EC amount, *n*/patient, median (IQR)	2 (2–3)	3 (n.a.)	2 (2–3)	0.205
Intraoperative transfusion y/n, *n*[a] (%)	200 (38.4)	44 (35.8)	156 (39.2)	0.423
Intraoperative EC amount, *n*/patient, median (IQR)	2 (2–3)	2 (1–3)	2 (2–3)	0.270
Postoperative transfusion y/n, *n*[a] (%)	175 (33.6)	35 (28.5)	140 (35.2)	0.138
Postoperative EC amount, *n*/patient, median (IQR)	2 (1–3)	2 (1–3)	2 (1–4)	0.717
FFP transfusion				
Overall transfusion y/n, *n*[a] (%)	127 (24.4)	28 (22.8)	99 (24.9)	0.574
Amount, *n*/patient, median (IQR)	4 (4–7)	4 (3–8)	4 (4–7)	0.558
Preoperative transfusion y/n, *n*[a] (%)	1 (0.2)	1 (0.8)	0 (0)	0.239
Preoperative FFP amount, *n*/patient, median (IQR)	2 (2–2)	2 (2–2)	0 (0–0)	n.a.

Table 2 (continued)

Complication	Overall, *n*[a] (%)	NMIBC, *n*[a] (%)	MIBC, *n*[a] (%)	*p* value
Intraoperative transfusion y/n, *n*[a] (%)	94 (18)	21 (17.1)	73 (18.3)	0.695
Intraoperative FFP amount, *n*/patient, median (IQR)	4 (4–6)	4 (4–7)	4 (4–6)	0.596
Postoperative transfusion y/n, *n*[a] (%)	53 (10.2)	11 (8.9)	42 (10.6)	0.571
Postoperative FFP amount, *n*/patient, median (IQR)	4 (3–8)	3 (2–4)	4 (4–8)	0.007*
Thrombocyte transfusion				
Overall transfusion y/n, *n*[a] (%)	9 (1.7)	2 (1.6)	7 (1.8)	0.633
Amount, *n*/patient, median (IQR)	2 (1–2)	2 (n.a.)	2 (1–2)	0.889
Preoperative transfusion y/n, *n*[a] (%)	0 (0)	0 (0–0)	0 (0–0)	n.a.
Preoperative TC amount, *n*/patient, median (IQR)	0 (0)	0 (0–0)	0 (0–0)	n.a.
Intraoperative transfusion y/n, *n*[a] (%)	6 (1.2)	2 (1.6)	4 (1)	0.633
Intraoperative TC amount, *n*/patient, median (IQR)	2 (1–2)	2 (n.a.)	2 (1–2)	1.000
Postoperative transfusion y/n, *n*[a] (%)	3 (0.6)	0 (0)	3 (0.8)	1.000
Postoperative TC amount, *n*/patient, median (IQR)	2 (n.a.)	0 (0–0)	2 (n.a.)	n.a.

NMIBC, non-muscle-invasive bladder cancer; MIBC, muscle-invasive bladder cancer; IQR, interquartile range; CDC, Clavien Dindo Classification; EC, erythrocyte concentrate; TC, thrombocyte concentrate; FFP, fresh frozen plasma. * Indicates statistical significance. [a]Numbers reflect the number of patients (percentages).

Table 3. Univariate regression analyses of variables associated with 30-day morbidity after RC for NMIBC and RC for MIBC, respectively

Variables	Endpoint: 30-day CDC grade 3b to 5 after RC for NMIBC (events *n* = 43)		Endpoint: 30-day CDC grade 3b to 5 after RC for MIBC (events *n* = 152)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
BMI = 18.5–24.9 (Ref. Cat.)		<0.028*		0.002*
BMI = 25–29.9	1.366 (0.677–4.666)	0.243	1.083 (0.670–1.750)	0.744
BMI >30	3.753 (1.407–10.010)	0.008*	2.421 (1.415–4.144)	0.001*
Preoperative medical anticoagulation	2.401 (1.116–5.167)	0.025*	2.481 (1.630–3.777)	<0.001*
ASA score	2.535 (1.335–4.815)	0.004*		<0.001*
ASA score = 2	n.a.[a]	n.a.[a]	1.134 (0.348–3.701)	0.834
ASA score = 3	n.a.[a]	n.a.[a]	2.636 (0.822–8.449)	0.103
ASA score = 4	n.a.[a]	n.a.[a]	4.500 (0.972–20.827)	0.054
T-stage at RC	1.076 (0.899–1.290)	0.424	1.097 (0.976–1.233)	0.122
N-stage at RC	1.034 (0.322–3.318)	0.955	1.061 (0.834–1.350)	0.629
R-Stage at RC	0.617 (0.119–3.198)	0.565	1.221 (0.766–1.947)	0.401
Urinary diversion	0.916 (0.596–1.407)	0.689	0.815 (0.616–1.078)	0.151
Age	1.021 (0.981–1.063)	0.302	1.031 (1.010–1.053)	0.004*
Gender (male)	1.123 (0.462–2.728)	0.798	1.217 (0.748–1.978)	0.429

OR, odds ratio; CI, confidence interval; Ref. Cat., reference category; CDC, Clavien Dindo Classification; ASA, American Society of Anaesthesiologists; BMI, body mass index. * Indicates statistical significance. [a] No categorical analysis due to small sample size in single groups.

Discussion

The current study provides a detailed characterization of patients, who underwent RC for NMIBC and of those, who underwent RC for MIBC. The two groups were compared with regard to patient characteristics, complication rates, and survival rates in a tertiary German university hospital. To the best of our knowledge, this is the first study to identify risk factors for suffering a severe short-term complication after RC for NMIBC.

Overall, we found no differences regarding complication rates and complication severity between RC for

NMIBC and RC for MIBC, which indicates a similar perioperative risk for both groups. This is substantiated by the fact that the BMI and ASA score, both factors that have been shown to impact morbidity and mortality after RC, were also similar between the two groups [7, 13, 14]. The higher rates of early-bleeding complications and blood transfusions in MIBC patients are most likely due to larger tumors with higher tumor stages, which might increase the risk of bleeding and complicate surgery. Also, preoperative Hb values were significantly lower in MIBC patients, which may increase the risk for transfusion even further.

We found higher long-term complication rates affecting the urinary diversion in NMIBC patients. It is noteworthy that more continent urinary diversions were performed in those patients ($p = 0.040$). Both an NB and an IP are considered particularly challenging and surgical complex urinary diversions. Hence, the rates of short-term and long-term morbidity described in the literature are higher than with incontinent urinary diversions [15–18]. However, the total number and severity of complications were comparable between the two groups.

The current study confirmed a survival benefit with significantly higher CSS and OS rates for NMIBC patients. These findings have also been described in the literature and can reliably be explained with significantly higher tumor stages, positive surgical margins, lymphovascular infiltration rates, and positive lymph nodes with MIBC, which, as such, have already been identified as prognostic factors in prior studies [19–22]. Figure 1 displays overall survival after RC for NMIBC and RC for MIBC, respectively.

To date, it still remains challenging to select those NMIBC patients, who most likely will benefit from RC. In order to approach this issue, Sylvester et al. retrospectively analyzed 3,401 patients and identified tumor stage, grading, concomitant CIS, number of tumors, tumor size, and age as independent risk factors for tumor progression [3]. Based on these factors, the European Association of Urology Non-Muscle-invasive Bladder Cancer Guideline Panel provided an updated and widely accepted risk classification that subdivides patients into those with low-, intermediate-, high-, and very-high-risk for tumor progression [4]. RC is generally recommended in very-high-risk patients and should also be considered in high-risk patients, especially in those with BCG-unresponsive or BCG-relapsing tumors [4]. Another aspect that emphasizes the importance of RC as the preferred treatment choice for selected NMIBC patients is the low-staging accuracy of the initial TUR-B. This may result in understaging of a significant proportion of patients, who in fact have a muscle-invasive tumor stage rather than an NMIBC. Intravesical instillation therapy may be an inappropriate, oncologically inferior therapy for those patients. With that said, histological upstaging was evident in a significant proportion of both NMIBC patients and MIBC patients (38.2% and 58%), which is in accordance with the literature [23, 24]. On the other hand, RC remains a challenging surgical procedure with significant short-term morbidity and a high burden of disease for the individual patient. Therefore, a potential survival benefit is faced with surgical risks and potential (long-term) complications associated with RC.

To the best of our knowledge, this is the first study investigating risk factors for developing a severe complication after RC specifically in the context of RC for NMIBC. Obesity (BMI >30), comorbidity level (objectivied by the ASA score), and preoperative medical anticoagulation were identified as risk factors for the development of a severe complication (≥CDC IIIb) within 30 days after RC for NMIBC in the current study. Those factors, together with a higher age at surgery, were also identified as risk factors for severe complications in the context of RC for MIBC.

A higher BMI and a higher comorbidity level have already been found as risk factors for major short-term complications after RC in various studies [7, 25–30]. This is quite understandable, since both factors complicate surgery and reduce the regeneration capacity of the patient. A preoperatively necessary medical anticoagulation may also be interpreted as an indirect indicator for the cardiovascular health of the patient and, depending on the restart date of application postsurgery, may be causative for bleeding complications that ultimately necessitate revision surgery.

In order to offer the best possible treatment for an individual NMIBC patient, it is crucial to weigh those factors in the decision-making process and counsel patients accordingly. On average, we performed 52 RCs per year throughout the study period, which is considered a high-volume hospital for RC. Being a university hospital, only 5 of the 13 operating surgeons had performed a significant number of RCs prior to the beginning of the study period. The remaining 8 surgeons started to perform RCs during the study period. A systematic review including 39 studies was conducted to investigate the impact of hospital volume (HV) and surgeon volume on perioperative morbidity after RC. While the authors found improved primary and secondary outcomes (lower in-hospital, 30-, and 90-day mortality, lower complication rates, lower

positive surgical margins, higher LND) with a high HV (at least 10 RCs annually in most included studies), the data on surgeon volume was conflicting and not conclusive [31]. As a consequence, The European Association of Urology Muscle-invasive and Metastatic Bladder Cancer Guideline Panel recommends hospitals to perform at least 10, and preferably more than 20, RCs annually. Therefore, our HV seems to be sufficiently high [32].

The current study has some limitations. We analyzed the available data based on our medical database. Although the medical records comprise data on inpatient stays and subsequent presentations via the emergency department, the outpatient clinic, or the oncologic ward, we can only report on "observed complications" of patients that were treated at our institution. Therefore, the study bears a risk for recall bias and underreporting, which is especially true, when it comes to long-term follow-up. Hence, short-term complications were classified more precisely and in greater detail than long-term complications. This is also due to the fact that a relevant proportion of (low-grade) complications is being dealt with by the treating urologist on an outpatient basis. However, rather severe complications necessitating an inpatient stay or surgery are usually referred to our hospital, even if they occur in the long term. Also, a significant proportion of patients was seen in the outpatient clinic of our institution or the oncologic ward on a regular basis and missing information was gathered as thorough and accurate as possible.

Conclusion

Patients who underwent RC for NMIBC are exposed to a comparably high perioperative risk than patients with MIBC. RC seems to be a viable treatment option for certain NMIBC patients with a significant histological upstaging in both groups. In patients with obesity, a high ASA score, and with medical drug anticoagulation, the indication for surgery should be confirmed especially strict and possible treatment alternatives should be considered particularly thorough.

Statement of Ethics

The study was approved by the University of Regensburg Local Ethics Committee (ethic vote: 19-1481-104). It was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written consent was not obtained, since all data were collected in a retrospective manner as part of routine diagnosis and treatment and analyzed anonymously. The need for informed consent was waived by the University of Regensburg Local Ethics Committee.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Maximilian Haas: project development, data management, data analysis, and manuscript writing. Charlotte Knobloch: data collection and data analysis. Roman Mayr and Michael Gierth: data collection and manuscript writing. Christoph Pickl and Simon Engelmann: data collection and data management. Stefan Denzinger: data collection, data analysis, and manuscript editing. Maximilian Burger: data management and resources. Johannes Breyer: project development and manuscript writing. Sonja Holbach: project development, data collection, data management, and manuscript editing.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

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