available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Bladder Cancer

Editorial by John S. McGrath, Angela B. Smith and Stephen B. Williams on pp. 66-67 of this issue

Improving Estimates of Perioperative Morbidity After Radical Cystectomy Using the European Association of Urology Quality Criteria for Standardized Reporting and Introducing the Comprehensive Complication Index

Malte W. Vetterlein [†,‡,*], *Jakob Klemm* [†], *Philipp Gild, Marlon Bradtke, Armin Soave, Roland Dahlem, Margit Fisch, Michael Rink* [‡]

Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Article info

Article history:
Accepted August 8, 2019

Associate Editor:
James Catto

Keywords:
Clavien-Dindo classification
Comorbidity
Postoperative complications
Quality improvement
Urinary bladder neoplasms

Abstract

Background: No procedure-specific definitions in complication reporting have been universally accepted in urological surgery, and conventional classification systems do not reflect cumulative morbidity.
Objective: To conduct a rigorous assessment of 30-d complications after radical cystectomy and improve morbidity estimates by introducing the novel Comprehensive Complication Index (CCI).
Design, setting, and participants: A retrospective proof-of-concept study of 506 patients with bladder cancer between 2009 and 2017.
Intervention: Radical cystectomy with pelvic lymph node dissection.
Outcome measurements and statistical analyses: Thirty-day complications were extracted from digital charts based on a procedure-specific catalog. Each complication was graded by the Clavien-Dindo classification (CDC), and each individual CCI was calculated. We evaluated traditional morbidity endpoints and tested the ability of both classification tools to mirror cumulative morbidity. Multivariable regression analyses were employed for risk modeling using conventional and novel endpoints. The study fulfilled all the European Association of Urology (EAU) criteria of standardized reporting. Limitations include restricted follow-up of 30 d.
Results and limitations: Of 506 patients, 503 (99%) experienced a total of 2485 complications, of which the majority was classified as "minor" (CDC grade $\leq$ IIIa; 89%). Overall, 29 (5.7%), 20 (4.0%), and 12 (2.4%) patients were reoperated, readmitted, and died within 30 d, respectively. When using the CCI to capture cumulative morbidity, the proportion of patients with most severe complication burden (CDC grade $\geq$ IIIb or corresponding CCI $>$ 33.7) increased to 31% as compared with 11% when considering only the highest-grade complication according to the CDC. Age-adjusted comorbidity and delta hemoglobin were the main drivers of perioperative complications for all outcomes in multivariable models.
Conclusions: The assessment of short-term morbidity after radical cystectomy may be refined and optimized by employing the EAU criteria of standardized reporting and using the CCI to capture cumulative morbidity. These are the cornerstones of urgently needed procedure-tailored benchmarking to improve comparability and quality control.
Patient summary: Characterization of short-term morbidity after radical cystectomy was improved by using several validated assessment tools and adhering to existing guidelines for reporting surgical complications.

[†] These authors contributed equally.
[‡] These authors are members of the Urothelial Cancer Working Party of the European Association of Urology Young Academic Urologists.
[*] Corresponding author. Department of Urology, University Medical Center Hamburg-Eppendorf, Martinistr. 52, Hamburg 20246, Germany.
E-mail address: malte.vetterlein@gmail.com (M.W. Vetterlein).

https://doi.org/10.1016/j.eururo.2019.08.011
0302-2838/

1. Introduction

Almost 2 decades ago, Martin and colleagues [1] introduced 10 critical elements of comprehensive reporting of surgical complications and recommended to use a standardized reporting methodology. This concept was transferred into urology [2] and was most recently adopted by the European Association of Urology (EAU) within the framework of a guideline for complication reporting [3]. Radical cystectomy (RC) [4] represents a heavily impairing surgical procedure with significant short-term morbidity [5–8]. To assess such morbidity, the Clavien-Dindo classification (CDC) [9,10] has widely been adopted and validated in urological surgery [11]. Nevertheless, it still suffers from significant inter-rater variability [11,12], and more importantly, no universally accepted definitions for procedure-specific complications exist in the RC setting, resulting in a lack of comparable, reproducible, and unbiased assessment of outcomes. A major pitfall of the CDC is its inability to mirror a patient's cumulative morbidity burden, given that only the highest complication is graded. Thus, even if the CDC is used, the perceived morbidity is still prone to significant under-reporting. To address this problem, Slankamenac and colleagues [13] created the Comprehensive Complication Index (CCI), which synthesizes all complications into a single formula weighted by their severity. Despite its obvious strengths and complementary value to using the CDC alone [14,15], the introduction of the CCI into urology is limited to date [16]. Against this backdrop, our aim was threefold: (1) to generate a predefined catalog of general and RC procedure–specific complications, (2) to conduct a rigorous assessment of 30-d morbidity after RC according to the updated EAU guideline [3], and (3) to compare the CDC with the CCI. We hypothesized that the morbidity burden after RC is significantly higher than previously reported when applying strict definitions of adverse events, and that certain underestimation of morbidity may be avoided by using the novel CCI.

2. Patients and methods

2.1. Study population

This observational study was approved by the local ethics committee of Hamburg (No. PV5634). We performed a retrospective analysis of prospectively collected morbidity data from our institution, capturing individuals who had undergone open RC and bilateral pelvic lymph node dissection for bladder cancer between January 1, 2009 and December 31, 2017. None of the patients received neoadjuvant chemotherapy (N = 4 were excluded) or radiotherapy. The detailed perioperative workflow is described in the Supplementary material(Methods) .

2.2. Definition, extraction, and grading of complications

Prior to data extraction, four members of our working group predefined a complication catalog including adverse events after RC. Selection of complications was based on a critical review of the literature including landmark studies regarding morbidity assessment after RC [5–8]. Subsequently, an explicit definition was framed for each possible event employing the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (Supplementary Table 1). Complications were extracted from digitalized charts (Soarian Clinicals).

The collection and grading of complications followed several steps. First, any complication within the first 30 d after RC was recorded for each patient and each complication was graded according to the validated and adapted CDC [9,10]. Second, the 30-d CCI [13] was calculated for each patient using the online calculator provided on https://www.assessurgery.com. Based on the CDC, the CCI represents the perioperative course in a scale ranging from 0 (uneventful course) to 100 (death).

2.3. Clinical, surgical, and pathological characteristics

First, clinical characteristics were defined as age, gender, body mass index, age-adjusted Charlson comorbidity index (ACCI) [17,18], smoking status, preoperative hydronephrosis, preoperative hemoglobin (Hb), estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [19], the CKD stage according to the National Kidney Foundation, prior pelvic or abdominal surgery and radiotherapy, and prior systemic chemotherapy for malignancies other than bladder cancer. Second, surgical characteristics were defined as operative time and type of urinary diversion. Third, pathological characteristics such as tumor and nodal stage according to the most recent tumor, node, metastasis classification system, lymphovascular invasion, lymph nodes characteristics, and extracapsular extension were assessed as previously described (Table 1) [20].

2.4. Statistical analyses

First, descriptive analyses focused on clinical, surgical, and pathological features to characterize our RC population. We stratified our cohort by comorbidity burden using ACCI cutoffs ($\leq$2, 3–5, and $\geq$6) as previously validated for RC [18]. For comparisons between the groups, chi-square test, Fisher's exact test, and Kruskal-Wallis test were employed as appropriate.

Second, to comply with the EAU quality criteria of standardized reporting (Table 2), we defined and reported five morbidity key estimates (overall complications, most severe complications CDC grade $\geq$ IIIb, readmissions, reoperations, and mortality).

Third, we aimed to assess the ability of two different reporting methodologies (CDC vs CCI) to capture perioperative morbidity burden after RC using a two-step approach. Briefly, we calculated the median CCI considering only the highest complication (ie, according to the CDC) versus all complications. Additionally, we evaluated whether the ranking of complications changed if morbidity was summarized by the CCI in comparison with the CDC. We compared the proportion of patients with most severe (CDC

Table 1 – Clinical characteristics of 506 patients who underwent open radical cystectomy for carcinoma of the urinary bladder between January 2009 and December 2017.

	Overall	ACCI ≤2	ACCI 3–5	ACCI ≥6	*p* value
Clinical preoperative characteristics					
Number of patients (%)	506 (100)	173 (34)	260 (52)	73 (14)	–
Age (yr), median (IQR)	69 (62–74)	59 (53–65)	73 (68–76)	73 (71–79)	<0.001
Gender: male, *N* (%)	398 (79)	126 (73)	208 (80)	64 (88)	0.027
BMI, median (IQR)	26 (24–29)	26 (24–29)	26 (24–29)	25 (24–29)	0.8
Smoking status, *N* (%)					0.2
Never	67 (13)	18 (10)	36 (14)	13 (18)	
Ever	313 (62)	118 (69)	156 (60)	39 (53)	
Unknown	126 (25)	36 (21)	69 (26)	21 (29)	
Hydronephrosis, *N* (%)	80 (16)	24 (14)	42 (16)	14 (19)	0.6
Hemoglobin (g/dl), median (IQR)	14 (12–15)	14 (13–15)	13 (12–14)	13 (11–14)	<0.001
eGFR (ml/min/1.73 m^2), median (IQR)	73 (57–87)	84 (70–96)	67 (56–84)	55 (38–71)	<0.001
CKD stage according to the NKF, *N* (%)					<0.001
Stage 1–2, eGFR ≥60 ml/min/1.73 m^2	357 (71)	149 (86)	176 (68)	32 (44)	
Stage 3–5, eGFR <60 ml/min/1.73 m^2	149 (29)	24 (14)	84 (32)	41 (56)	
Prior pelvic or abdominal surgery, *N* (%)	168 (33)	34 (20)	109 (42)	25 (34)	<0.001
Prior pelvic or abdominal radiotherapy, *N* (%)	29 (5.7)	2 (1.2)	16 (6.2)	11 (15)	<0.001
Prior systemic chemotherapy[a], *N* (%)	8 (1.6)	1 (0.58)	3 (1.2)	4 (5.5)	0.027
Surgical characteristics					
Operative time (min), median (IQR)	278 (225–334)	314 (263–361)	264 (210–313)	241 (185–305)	<0.001
Urinary diversion type, *N* (%)					<0.001
Continent	136 (27)	97 (56)	36 (14)	3 (4.1)	
Incontinent	370 (73)	76 (44)	224 (86)	70 (96)	
Urinary diversion subtype, *N* (%)					<0.001
Ileal neobladder	99 (20)	68 (39)	28 (11)	3 (4.1)	
Ileal conduit	278 (55)	65 (38)	177 (68)	36 (49)	
Mainz Pouch I	35 (6.9)	28 (16)	7 (2.7)	0 (0)	
Colon conduit	5 (0.99)	3 (1.7)	1 (0.38)	1 (1.4)	
Cutaneous ureterostomy	87 (17)	8 (4.6)	46 (18)	33 (45)	
Mainz Pouch II	2 (0.40)	1 (0.58)	1 (0.38)	0 (0)	
Length of stay (d), median (IQR)	15 (13–18)	15 (13–17)	15 (13–18)	15 (12–18)	0.6
Pathological characteristics					
pT stage, *N* (%)					0.3
pT0	67 (13)	27 (16)	29 (11)	11 (15)	
pTa	21 (4.2)	8 (4.6)	10 (3.9)	3 (4.1)	
pTis	44 (8.7)	17 (9.8)	22 (8.5)	5 (6.9)	
pT1	46 (9.1)	13 (7.5)	27 (10)	6 (8.2)	
pT2	112 (22)	42 (24)	59 (23)	11 (15)	
pT3	144 (28)	40 (23)	84 (32)	20 (27)	
pT4	72 (14)	26 (15)	29 (11)	17 (23)	
pN stage, *N* (%)					0.4
pN0	342 (68)	119 (69)	177 (68)	46 (63)	
pN+	150 (30)	52 (30)	73 (28)	25 (34)	
pNx	14 (2.8)	2 (1.2)	10 (3.9)	2 (2.7)	
Organ confinement, *N* (%)					0.5
≤pT2 and pN0	254 (50)	93 (54)	130 (50)	31 (43)	
≥pT3 and/or pN+	246 (49)	78 (45)	127 (49)	41 (56)	
≤pT2 and pNx	6 (1.2)	2 (1.2)	3 (1.2)	1 (1.4)	
Lymphovascular invasion, *N* (%)	134 (26)	44 (25)	70 (27)	20 (27)	0.2
Number of lymph nodes removed, median (IQR)	13 (8–20)	16 (12–25)	12 (7–19)	10 (6–14)	<0.001
Lymph node density in pN + patients (in %), median (IQR)	17 (7–31)	15 (7–23)	18 (8–40)	20 (13–27)	0.2
Extracapsular extension in pN + patients, *N* (%)	45 (30)	14 (27)	22 (30)	9 (36)	0.6

ACCI = age-adjusted Charlson comorbidity index; BMI = body mass index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; IQR = interquartile range; NKF = National Kidney Foundation.
Percentages may not add up to 100%, as they are rounded.
[a] Refers to chemotherapy administered for malignancies other than carcinoma of the urinary bladder.

grade ≥ IIIb) [9] highest complications with the proportion of patients with the corresponding CCI of >33.7. Of note, given the specific weighting algorithm of the CCI [13], each CDC grade can be transferred into a corresponding CCI value threshold.

Fourth, we employed three multivariable regression models to identify covariates associated with a higher morbidity burden. Logistic regression models were used with CDC grade ≥ IIIb and the corresponding CCI threshold of >33.7 as bivariate endpoints. A multivariable tobit regression model [21] was used with CCI as a linear endpoint accounting for floor and ceiling effects at 0 and 100.

All statistical analyses were performed using Stata (StataCorp. 2015, Stata Statistical Software: release 14; StataCorp LP, College Station, TX, USA). The reported

Table 2 – Characterization of the European Association of Urology quality criteria for accurate and comprehensive reporting of surgical outcome and their implementation in 506 patients undergoing radical cystectomy between 2009 and 2017.

	EAU quality criteria	Implementation
1	Define the method of accruing data	Retrospective chart review and data extraction of digitalized charts (Soarian Clinicals)
2	Define who collected the data	A resident in urology and two medical students, who were not involved in the patients' treatment course, collected data
3	Indicate the duration of follow-up	Duration of follow-up was 30 d after radical cystectomy
4	Include outpatient information	Outpatient information was included
5	Include mortality data and causes of death	Mortality and causes of death were reported
6	Include definitions of complications	A predefined complication catalog including definitions of general and procedure-specific complications was generated
7	Define procedure-specific complications	
8	Report intra- and postoperative complications separately	Intra- and postoperative complications were considered separately
9	Use a severity grading system for postoperative complications (avoiding the distinction minor/major)	The Clavien-Dindo classification and the Comprehensive Complication Index were used
10	Postoperative complications should be presented in a table either by grade or by complication type (specific grades should always be provided; grouping is not accepted)	A detailed table of postoperative complications, including grading, treatment, frequencies, and proportions was provided
11	Include risk factors	The age-adjusted Charlson comorbidity index and other well-known risk factors were included into analyses
12	Include readmissions and causes	Readmissions and causes were tabulated
13	Include reoperations, types, and causes	Reoperations, types, and causes were tabulated
14	Include the percentage of patients lost to follow-up	Follow-up was available for all patients, given the retrospective review of digitalized charts and 30-d follow-up period.

EAU = European Association of Urology.

p values were two sided and values <0.05 were considered statistically significant.

3. Results

3.1. Descriptive analyses of clinical, surgical, and pathological characteristics

All patient characteristics and their categorization are depicted in Table 1. Our study population comprised 506 patients with a median age of 69 yr (interquartile range [IQR] 62–74), 398 (79%) patients were male, and the median ACCI was 3 (IQR 2–4). Median operative time was 278 min (IQR 225–334), and 278 patients (55%) underwent RC with ileal conduit diversion, followed by 99 patients (20%) with a neobladder and 87 patients (17%) with a cutaneous ureterostomy. The distribution of localized (≤pT2N0) and locally advanced disease (≥pT3 and/or pN+) was balanced, with 254 (50%) and 246 (49%) patients, respectively. Among the ACCI strata, men had a higher comorbidity burden than women, and operative time and use of continent diversions decreased with a greater ACCI (all $p < 0.03$). Of note, the median number of removed lymph nodes decreased with greater ACCI ($p < 0.001$).

3.2. Assessment of perioperative 30-d complications

A detailed summary of the number and proportion of all recorded complication types, categories, and grading according to the CDC is shown in Table 3. Overall, 2485 complications were captured in 503 of 506 patients (99%; 95% confidence interval [CI] = 98–100%), which translated into a median of five (IQR 3–6) complications per patient (Supplementary Fig. 1). Genitourinary (24%), gastrointestinal (19%), and infectious complications (15%) were the most common complication types, whereas

Table 3 – Frequencies, proportions, therapeutic management, and grading of perioperative 30-d complications in 506 patients who underwent open radical cystectomy between January 2009 and December 2017.

	CDC grading	Management	Number of complications	Proportion, % (*N* = 506)
Gastrointestinal				
482 complications (19%)[a] in 323 patients				
Ileus (paralytic)	I	Conservative; cessation of oral intake and i.v. fluid support	24	4.7
	IIIa	Replacement of nasogastric tube	12	2.4
Small bowel obstruction (mechanical)	IIIb	Laparotomy	3	0.59
Constipation	I	Conservative; laxatives, i.v. fluid support	131	26
Clostridium difficile colitis	II	Antibiotic treatment	16	3.2
Gastrointestinal bleeding	I	Conservative; clinical observation or diagnostic evaluation only	1	0.20
	II	Blood transfusion	0	–

Table 3 (*Continued*)

	CDC grading	Management	Number of complications	Proportion, % (*N* = 506)
	IIIb	Esophagogastroduodenoscopy	2	0.40
Emesis	I	Conservative; antiemetics and i.v. fluid support	164	32
Anastomotic bowel leak	IIIb	Laparotomy	2	0.40
Diarrhea (≠*C. difficile* associated)	I	Conservative; antidiarrheals, i.v. fluid support, electrolytes	127	25
Infectious				
380 complications (15%)[a] in 357 patients				
Fever of unknown origin	II	Conservative; antipyretics, antibiotic treatment	20	4.0
Bacteriuria (>10^5 cfu/ml; asymptomatic)	I	Conservative; no antibiotic treatment	28	5.5
Urinary tract infection (>10^5 cfu/ml; symptomatic)	II	Antibiotic treatment	316	62
Abscess	II	Antibiotic treatment	1	0.20
	IIIa	Incision and drainage	0	–
	IIIb	Incision and drainage + general anesthesia	0	–
Sepsis (SIRS in response to infectious process)	II	Antibiotic treatment, supportive care	1	0.20
	IVa	Septic single organ dysfunction, ICU	5	1.0
	IVb	Septic multiorgan dysfunction, ICU	2	0.40
	V	Septic multiorgan dysfunction leading to death	2	0.40
Pyelonephritis	II	Antibiotic treatment	1	0.20
Diverticulitis	II	Antibiotic treatment	1	0.20
Gastroenteritis	II	Conservative; antiemetics, antibiotic treatment	2	0.40
Cholecystitis	IIIb	Cholecystectomy	1	0.20
Wound				
98 complications (3.9%)[a] in 83 patients				
Wound seroma	I	Conservative; clinical observation or diagnostic evaluation only	0	–
Wound infection (SSI)	II	Antibiotic treatment	23	4.6
Wound dehiscence (fascia intact)	I	Conservative; clinical observation or diagnostic evaluation only, reinforced adhesive skin closure	56	11
	IIIb	Secondary surgical closure	5	1.0
Fascial dehiscence/evisceration	IIIb	Secondary surgical closure	14	2.8
Genitourinary				
590 complications (24%)[a] in 408 patients				
Acute kidney injury	I	Conservative; i.v. fluid support, diuretics	21	4.2
	IVa	Dialysis	2	0.40
Hydronephrosis/ureteral obstruction (new onset)	I	Conservative; clinical observation or diagnostic evaluation only	206	41
Urinary leak/urinoma	I	Conservative; clinical observation or diagnostic evaluation only, deferred Foley catheter extraction	10	2.0
	IIIa	Drainage	2	0.40
	IIIb	Ureter reimplantation/ retrograde ureteral stenting	3	0.60
Urinary retention	I	Conservative; clinical observation or diagnostic evaluation only, replacement of Foley catheter (neobladder/ pouch)	5	1.0
Parastomal hernia	I	Conservative; clinical observation or diagnostic evaluation only	0	–
	IIIb	Laparotomy and surgical revision	0	–
Urostomy ischemia	I	Conservative; clinical observation or diagnostic evaluation only	0	–

Table 3 (*Continued*)

	CDC grading	Management	Number of complications	Proportion, % (*N* = 506)
	IIIb	Laparotomy and surgical revision	0	–
Hematuria	I	Conservative; clinical observation or diagnostic evaluation only	341	67
Cardiac				
132 complications (5.3%)[a] in 110 patients				
Arrhythmia	II	Conservative; medical cardioversion	28	1.1
	IIIb	Pacemaker, cardioversion	4	0.80
Myocardial infarction	IVa	Coronary angiography and stent implantation, ICU	6	1.2
Hypertension (new onset)	II	Antihypertensives	39	7.7
(Acute) congestive heart failure	IVa	Coronary angiography, ICU	9	1.8
Angina (pectoris)	I	Conservative; clinical observation or diagnostic evaluation only	8	1.8
Hypotension	II	Medical treatment	38	7.5
Pulmonary				
46 complications (1.9%)[a] in 38 patients				
Atelectasis	II	Continuous positive airway pressure, physiotherapy	0	–
Pneumonia	II	Antibiotic therapy	22	4.4
Respiratory distress/dyspnea	I	Oxygen, physiotherapy	15	3.0
Pneumothorax	I	Conservative; clinical observation or diagnostic evaluation only	0	–
	IIIa	Chest tube	1	0.20
Pleural effusion	I	Conservative; clinical observation or diagnostic evaluation only	8	1.6
	IIIa	Chest tube	0	–
Bleeding				
174 complications (7.0%)[a] in 157 patients				
Anemia requiring transfusion	II	Blood transfusion	134	26
Postoperative bleeding other than gastrointestinal	I	Conservative; clinical observation or diagnostic evaluation only	4	0.80
	II	Blood transfusion/fibrinogen	1	0.20
	IIIa	Suture ligation	1	0.20
	IIIb	Laparotomy and surgical revision	4	0.80
Wound hematoma	I	Conservative; clinical observation or diagnostic evaluation only	30	5.9
Thromboembolic				
22 complications (0.89%)[a] in 21 patients				
Deep vein thrombosis	II	Anticoagulation	8	1.6
Pulmonary embolism	I	Conservative; clinical observation or diagnostic evaluation only	1	0.20
	II	Anticoagulation	9	1.8
	IVa	ICU, anticoagulation	1	0.20
Superficial phlebitis	II	Conservative; heparin ointment	3	0.59
Neurological				
176 complications (7.1%)[a] in 171 patients				
Peripheral neuropathy	I	Conservative; clinical observation or diagnostic evaluation only	138	27
CVA/TIA	II	Antiplatelets, anticoagulation	5	1.0
Delirium/agitation	II	Antipsychotics	29	5.7
Vertigo	II	Medical therapy	0	–
Loss of consciousness/syncope	I	Conservative; clinical observation or diagnostic evaluation only	4	0.80
Seizure	II	Medical therapy	0	–
Intraoperative[b]				
1 complication (0.040%)[a] in 1 patient				
Vascular injury	–	–	0	–

Table 3 (*Continued*)

	CDC grading	Management	Number of complications	Proportion, % (N = 506)
Bowel injury	–	Revision surgery	1	0.20
Retained foreign body	–	–	0	–
Miscellaneous				
383 complications (15%)[a] in 292 patients				
Psychological illness	I	Conservative; psycho-oncological support	22	4.4
Dermatitis	I	Ointment	13	2.6
Acidosis	I	Conservative; medical therapy, electrolytes	3	0.59
Decubitus ulcer	I	Conservative	36	7.1
Lymphocele	I	Conservative; clinical observation or diagnostic evaluation only	19	3.8
	IIIa	Drainage	10	2.0
Dehydration	I	Conservative; i.v. fluid support	2	0.40
Edema	I	Conservative; medical therapy	206	41
Hypokalemia	I	Conservative; medical therapy	21	4.2
Other rare complications	I	Conservative	53	11

CDC = Clavien-Dindo classification; cfu = colony-forming units; CVA = cerebrovascular accident; ICU = intensive care unit; i.v. = intravenous; SIRS = systemic inflammatory response syndrome; SSI = surgical site infection; TIA = transient ischemic attack.
Percentages may not add up to 100%, as they are rounded.
[a] The percentage refers to the proportion of all 2485 complications.
[b] The CDC does not apply to intraoperative complications. Thus, no grading system was used.

wound, cardiac, pulmonary, bleeding, thromboembolic, and neurological events were relatively rare (all ≤7%). Overall, 55 patients (11%; 95% CI = 8.3–14%) suffered from most severe (CDC grade ≥ IIIb) complications requiring an intervention under general anesthesia. The distribution of complications according to the CDC is depicted in Fig. 1A. Overall, 492 (97%) patients developed more than one complication within 30 d after RC, and 170 (34%) developed more than five complications. Patients with higher grades in the CDC also had a higher number of complications, particularly if the CDC grade was ≤ IIIa (Fig. 1B). Most complications occurred within 14 d of RC (Fig. 1C).

Reoperations related to the primary surgery were performed in 29 patients (5.7%; 95% CI = 3.7–7.7%) and were most commonly wound related (Supplementary Table 2). Twenty patients (4.0%; 95% CI = 2.3–5.7%) were readmitted within 30 d. Major causes for readmission were infectious (50%) and gastrointestinal (21%) complications (Supplementary Table 3). Twelve patients (2.4%; 95% CI = 1.1–3.7%) died of various non–cancer-related causes within 30 d of surgery (Supplementary Table 4).

3.3. *Evaluation of the CCI and associations with 30-d morbidity*

Thirty days postoperatively, the median CCI taking into account only the highest complication was 21 (Supplementary Fig. 2A). This figure increased to 29 when considering all complications (Supplementary Fig. 2B). The median CCI increased significantly with every CDC grade (Fig. 2). Overall, 20% of patients were upgraded to most severe complication (CCI ≥33.7) when calculating their cumulative CCI considering all complications compared with the corresponding CCI taking into account only the highest complication.

In logistic regression analysis, ACCI (p = 0.020) and ΔHb (p = 0.011) [22] were associated with a CDC grade ≥ IIIb complication (Table 4), and results were similar for the other endpoints (Supplementary Table 5).

4. Discussion

We report a meticulous assessment of 30-d morbidity in a contemporary population of patients undergoing open RC for bladder cancer. Additionally, we implemented the revised EAU quality criteria for standardized reporting and evaluated the cumulative morbidity burden after RC by including the novel CCI. We found that almost every patient (99%) experienced at least one complication when a rigorously predefined complication catalog was used. Despite our complication rate being higher than that in other RC series in the literature [5–8], our findings are not surprising and underscore the utmost importance of thorough documentation and workup, as they have immediate clinical, administrative, and academic implications.

Significant deficiencies in complication reporting [23] and underestimation of low-grade complications [6] are apparent in the urological literature. The interobserver variability in grading and assigning complications [12] may be related to procedure-specific variability of complications. Thus, precision and creation of a procedure-specific morbidity spreadsheet is urgently needed in the RC setting to improve the reliability of grading complications according to their severity, particularly when investigating the conventional endpoint “overall complications.” This concept has, for example, been demonstrated par excellence by the Clinical Research Office of the Endourological Society

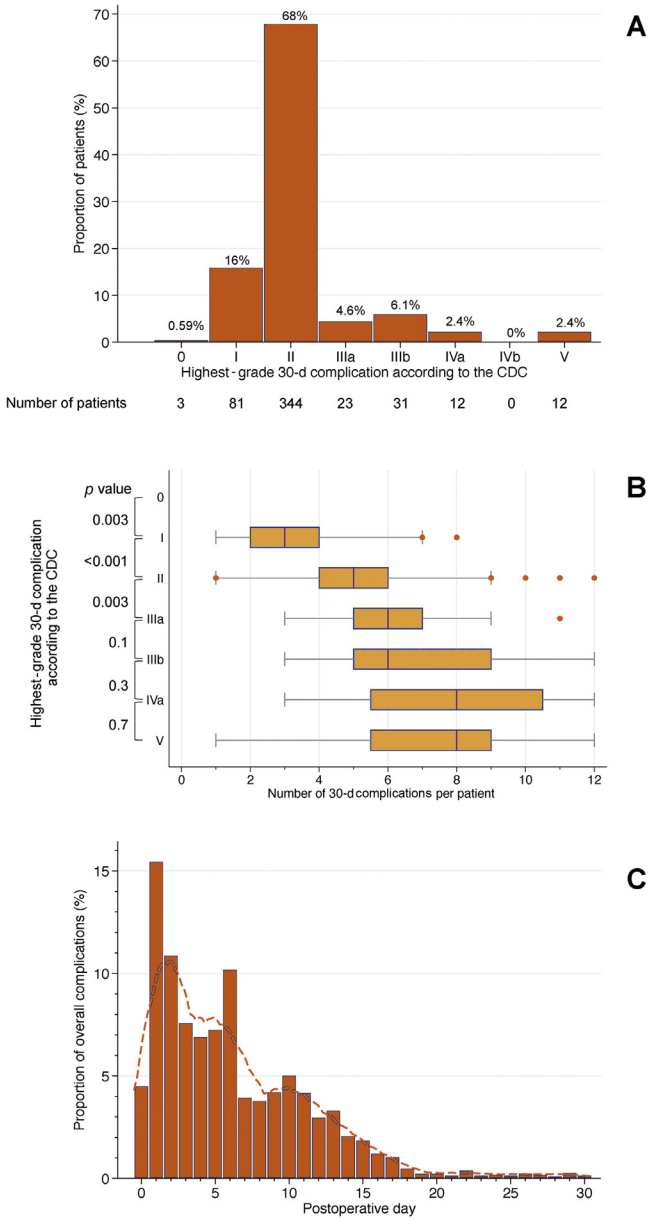

Fig. 1 – (A) Column charts depicting the distribution of the highest grade 30-d complication per patient and (B) whisker plots depicting the median number and interquartile range of 30-d complications per patient stratified by the Clavien-Dindo classification (CDC). Orange dots indicate outliers. Differences between CDC strata in Fig. 1B were calculated using the Mann-Whitney *U* test. (C) Histogram with kernel density plot (orange dashes) depicting the incidence of overall complications over 30 d following radical cystectomy.

Table 4 – Multivariable logistic regression model identifying associations of clinical characteristics and short-term morbidity after open radical cystectomy.

	Odds ratio (95% confidence intervals)	*P* value
Multivariable logistic regression: 30-d CDC grade ≥ IIIb vs CDC grade ≤ IIIa		
Gender		
Male	1 (Reference)	–
Female	1.07 (0.47; 2.40)	0.9
ACCI, continuous	1.21 (1.03; 1.41)	0.020
Body mass index, continuous	1.05 (0.99; 1.11)	0.079
ΔHb[a], continuous	1.05 (1.01; 1.09)	0.011
Prior pelvic or abdominal surgery		
No	1 (Reference)	–
Yes	0.65 (0.32; 1.31)	0.2
Urinary diversion type		
Continent	1 (Reference)	–
Incontinent	1.37 (0.56; 3.32)	0.5
CKD stage according to the NKF		
Stage 1–2, eGFR ≥60 ml/min/1.73 m^2	1 (Reference)	–
Stage 3–5, eGFR <60 ml/min/1.73 m^2	0.98 (0.48; 2.00)	>0.9
Organ confinement		
≤pT2 and pN0	1 (Reference)	–
≥pT3 and/or pN+	1.19 (0.61; 2.31)	0.6

ACCI = age-adjusted Charlson comorbidity index; CDC = Clavien-Dindo classification; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; NKF = National Kidney Foundation.
Formula: (preoperative Hb – postoperative nadir Hb)/preoperative Hb × 100.
[a] Percentage of change in preoperative and postoperative nadir Hb level.

Percutaneous Nephrolithotomy Study Group [24]. Indeed, accurate documentation and reporting of complications do not at all implicate treatment failure or inferior health care. On the contrary, these are rather tantamount to an element of quality control such as the implementation of a comprehensive outcome measures score to aid in regulation [25], which implies having an organization able to detect them, and should to be an integral part of qualification as a specialized certified referral center with uro-oncological expertise. Moreover, in times of increased rates of medical lawsuits, patient information and counseling regarding the frequency, but more importantly the significance, of complications is crucial.

In fact, both the quality and the quantity of a complication are paramount. It is debatable whether every single undesirable event should be considered a complication, particularly in the light of the vast majority of patients (84%) in our study presenting with no more than a highest grade I or II complication. Low-grade complications do not necessarily impair the postoperative course, although they may be bothering for a patient with potential impact on quality of life, which alone justifies conscientious documentation. We incorporated the CCI into perioperative evaluation with its strength in capturing cumulative morbidity, which, to our knowledge, has been a matter of debate only once in the context of RC [16]. We found significant upgrading of the recorded morbidity in over 20% of patients toward a CCI score of ≥33.7, corresponding to a CDC grade IIIb, often referred to as the threshold of a "major" or "most severe" complication [13]. Given the underlying mathematical basis and weighting approach, the impact of less severe complications is more adequately captured, but it diminishes on the CCI as more severe adverse events are included [13]. Thus, the CCI provides a more intuitive reflection of the perceived overall morbidity. The importance of this is further substantiated by our finding that the number of complications per patient increased significantly with each grade when comparing patients with no more than a "minor" complication (ie, CDC grade ≤ IIIa). Whether the increased morbidity as objectified by the CCI is mirrored by inferior patient-reported

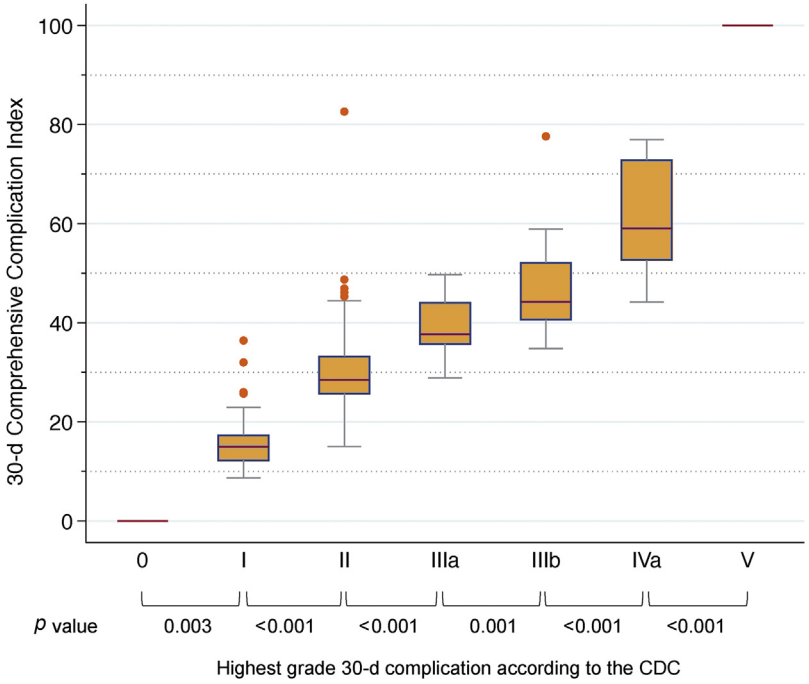

Fig. 2 – Whisker plots depicting the median 30-d CCI and interquartile range per patient stratified by the Clavien-Dindo classification (CDC). Orange dots indicate outliers. Differences between CDC strata were calculated using the Mann-Whitney *U* test. CCI = Comprehensive Complication Index.

outcomes, treatment satisfaction, and quality of life remains an intriguing research question for future prospective studies. Similarly, whether this effect is mirrored by more pronounced correlations of the CCI to objective surgical quality indicators such as treatment costs will be the subject of an upcoming evaluation. Until then, caution should be added regarding the exclusive use of the CCI, as more evidence is needed to validate its added value and a significant change over current methodologies. Conceivably, an increasing use of the novel CCI in future investigations may further be fueled by our confirmation of the feasibility to incorporate the CCI into risk modeling. Comorbidity-associated covariates such as ACCI and ΔHb were the main drivers of a higher perioperative morbidity burden for both conventional (CDC) and novel (CCI) endpoints.

Additionally, our findings have practical implications from an academic perspective. Reliable comparability across centers can only be guaranteed by implementing universally accepted, predefined complication checklists to mitigate extensive subjectivity, bias, and under-reporting. This is a fundamental prerequisite for the urgently needed multi-institutional benchmarking [26] of invasive urological procedures such as RC, as it has already been adopted very successfully in general surgery [27]. If we manage to define the best achievable results under ideal circumstances [26], this may be a starting point for further quality improvement cycles in the sense of "defining the best, comparing with the best, and learning from the best" [28].

Our study has limitations. Undoubtedly, there are complications known to occur >30 d after RC. We purposely used an a fortiori argument, that is, if extensive 30-d complication rates are found, morbidity will be even higher after longer time periods. However, it is undoubtedly of utmost importance to identify and define possible long-term procedure-specific complications, which do not emerge shortly after surgery. Moreover, we chose 30 d to be able to extract most possible granular data from our digitalized charts and to mitigate information loss during retrospective data extraction due to recall bias and documentation quality. However, we believe that this bias is small, as complications and grading had been defined before data extraction was initiated. As currently scheduled, a prospective, multi-institutional validation study will be needed to confirm our findings. Further, we were not able to identify intraoperative surgical complications in such detail that would be required when employing pre-existing scores [29,30], and these may be under-reported in our retrospective evaluation. The association between complications and quality of life may be clinically important, but was not investigated in this study. Our complication rates may not entirely be generalizable to a cohort undergoing neoadjuvant chemotherapy, and patients may have been readmitted to another hospital. Thus, we cannot entirely rule out a potential underestimation of readmissions. Finally, ΔHb in regression analyses [22] is prone to a "clock starting" bias (ie, the postoperative Hb nadir may occur after the event of interest). However, we believe that this bias is small. First, the actual definition of a complication according to the CDC is to notice an Hb drop initially and then intervene. Second, there were only four cases (0.80%) with bleeding complications requiring a reintervention (CDC grade IIIb), and the remainders were transfusions, underlining the predominant role of ΔHb as a surrogate of intraoperative blood loss.

5. Conclusions

Short-term morbidity after RC is dramatically higher than previously reported if the EAU quality criteria of standardized reporting are fulfilled and combined with a rigorous assessment of complications. This is particularly apparent in case of "minor" complications. Consequently, an expert consensus on procedure-specific complications is necessary to enable procedure-tailored benchmarking. Furthermore, estimates of cumulative morbidity are improved by additional use of the novel CCI as an adjunct to the CDC. The CCI appears to be a promising tool for future research to investigate its discriminative ability regarding subjective and objective outcome measures such as health-related quality of life, treatment satisfaction, and costs.

Author contributions: Malte W. Vetterlein had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Vetterlein, Klemm, Rink.
Acquisition of data: Vetterlein, Klemm, Bradtke.
Analysis and interpretation of data: Vetterlein, Klemm, Fisch, Rink.
Drafting of the manuscript: Vetterlein, Klemm, Rink.
Critical revision of the manuscript for important intellectual content: Gild, Bradtke, Soave, Dahlem.
Statistical analysis: Vetterlein, Klemm.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Fisch, Rink.
Other: None.

Financial disclosures: Malte W. Vetterlein certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Acknowledgment statement: Parts of the results of the current study were accepted and presented in abstract form at the EAU 2018 Annual Congress (March 16–20, 2018, Copenhagen, Denmark; DOI: 10.1016/S1569-9056(18)31210-7), the American Association of Genitourinary Surgeons 2018 Annual Meeting (April 26–29, 2018, Scottsdale, AZ, USA), the American Urological Association 2018 Annual Meeting (May 18–21, 2018, San Francisco, CA, USA; DOI: 10.1016/j.juro.2018.02.1489), and the 38th Congress of the Société Internationale d'Urologie (October 4–7, 2018, Seoul, Korea; DOI: 10.1007/s00345-018-2492-3).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2019.08.011.

References

[1] Martin 2nd RC, Brennan MF, Jaques DP. Quality of complication reporting in the surgical literature. Ann Surg 2002;235:803–13.
[2] Donat SM. Standards for surgical complication reporting in urologic oncology: time for a change. Urology 2007;69:221–5.
[3] Mitropoulos D., Artibani W., Graefen M., Remzi M., Rouprêt M., Truss M.C. EAU guidelines on reporting and grading of complications after urologic surgical procedures 2016. https://uroweb.org/guideline/reporting-complications.
[4] Alfred Witjes J, Lebret T, Comperat EM, et al. EAU guidelines on muscle-invasive and metastatic bladder cancer.Updated 2016 Eur Urol 2017;71:462–75.
[5] Shabsigh A, Korets R, Vora KC, et al. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. Eur Urol 2009;55:164–74.
[6] Novara G, De Marco V, Aragona M, et al. Complications and mortality after radical cystectomy for bladder transitional cell cancer. J Urol 2009;182:914–21.
[7] Roghmann F, Trinh QD, Braun K, et al. Standardized assessment of complications in a contemporary series of European patients undergoing radical cystectomy. Int J Urol 2014;21:143–9.
[8] Schiavina R, Borghesi M, Guidi M, et al. Perioperative complications and mortality after radical cystectomy when using a standardized reporting methodology. Clin Genitourin Cancer 2013;11:189–97.
[9] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.
[10] Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187–96.
[11] Mitropoulos D, Artibani W, Biyani CS, Bjerggaard Jensen J, Roupret M, Truss M. Validation of the Clavien-Dindo grading system in urology by the European Association of Urology Guidelines Ad Hoc Panel. Eur Urol Focus 2018;4:608–13.
[12] Poletajew S, Zapala L, Piotrowicz S, et al. Interobserver variability of Clavien-Dindo scoring in urology. Int J Urol 2014;21:1274–8.
[13] Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The Comprehensive Complication Index: a novel continuous scale to measure surgical morbidity. Ann Surg 2013;258:1–7.
[14] Slankamenac K, Nederlof N, Pessaux P, et al. The Comprehensive Complication Index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. Ann Surg 2014;260:757–62, discussion 762–763.
[15] Clavien PA, Vetter D, Staiger RD, et al. The Comprehensive Complication Index (CCI®): added value and clinical perspectives 3 years "down the line". Ann Surg 2017;265:1045–50.
[16] Furrer MA, Huesler J, Fellmann A, Burkhard FC, Thalmann GN, Wuethrich PY. The Comprehensive Complication Index CCI: a proposed modification to optimize short-term complication reporting after cystectomy and urinary diversion. Urol Oncol 2019;37(291):e299–18.
[17] Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245–51.
[18] Koppie TM, Serio AM, Vickers AJ, et al. Age-adjusted Charlson comorbidity score is associated with treatment decisions and clinical outcomes for patients undergoing radical cystectomy for bladder cancer. Cancer 2008;112:2384–92.
[19] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
[20] Marks P, Gild P, Soave A, et al. The impact of variant histological differentiation on extranodal extension and survival in node positive bladder cancer treated with radical cystectomy. Surg Oncol 2019;28:208–13.
[21] Twisk J, Rijmen F. Longitudinal tobit regression: a new approach to analyze outcome variables with floor or ceiling effects. J Clin Epidemiol 2009;62:953–8.
[22] Spolverato G, Kim Y, Ejaz A, Frank SM, Pawlik TM. Effect of relative decrease in blood hemoglobin concentrations on postoperative

morbidity in patients who undergo major gastrointestinal surgery. JAMA Surg 2015;150:949–56.
[23] Breau RH, Gaboury I, Scales Jr CD, Fesperman SF, Watterson JD, Dahm P. Reporting of harm in randomized controlled trials published in the urological literature. J Urol 2010;183:1693–7.
[24] de la Rosette JJ, Opondo D, Daels FP, et al. Categorisation of complications and validation of the Clavien score for percutaneous nephrolithotomy. Eur Urol 2012;62:246–55.
[25] Collins JW, Hosseini A, Wiklund PN. Validated comprehensive outcome measures will aid regulation. Eur Urol 2014;66:398–400.
[26] Ettorchi-Tardy A, Levif M, Michel P. Benchmarking: a method for continuous quality improvement in health. Healthc Policy 2012;7:e101–19.
[27] Schmidt HM, Gisbertz SS, Moons J, et al. Defining benchmarks for transthoracic esophagectomy: a multicenter analysis of total minimally invasive esophagectomy in low risk patients. Ann Surg 2017;266:814–21.
[28] Clavien PA, Puhan MA. Measuring and achieving the best possible outcomes in surgery. Br J Surg 2017;104:1121–2.
[29] Rosenthal R, Hoffmann H, Clavien PA, Bucher HC, Dell-Kuster S. Definition and classification of intraoperative complications (CLASSIC): Delphi study and pilot evaluation. World J Surg 2015;39:1663–71.
[30] Kaafarani HM, Mavros MN, Hwabejire J, et al. Derivation and validation of a novel severity classification for intraoperative adverse events. J Am Coll Surg 2014;218:1120–8.