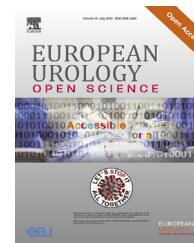


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European Association of Urology



## Bladder Cancer

# Morbidity and Days Alive and Out of Hospital Within 90 Days Following Radical Cystectomy for Bladder Cancer

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### Abstract

**Background:** Morbidity after radical cystectomy (RC) is usually quantified in terms of rates of complications, mortality, reoperations, and readmissions, and length of stay (LOS). The overall burden following RC within the first 90 d following RC may be better described using days alive and out of hospital (DAOH), which is a validated, patient-centred proxy for both morbidity and mortality.

**Objective:** To report short-term morbidity, LOS, and DAOH within 90 d after RC and risk factors associated with these parameters.

**Design, setting and participants:** The study included 729 patients undergoing RC for bladder cancer at a single academic centre from 2009 to 2019. Data were retrieved from national electronic medical charts.

**Outcome measurements and statistical analysis:** Multivariate analysis was used to investigate variables associated with a major complication, LOS >7 d, and DAOH <80 d.

**Results and limitations:** The 90-d complication rate was 80%, including major complications in 37% of cases. Median LOS was 7 d (interquartile range (IQR) 6–9) and median DAOH was 80 d (IQR 71–83) days. Body mass index and the Charlson comorbidity index (CCI) predicted major complications. CCI predicted LOS >7 d and DAOH <80 d.

**Conclusions:** RC was associated with significant short-term morbidity and DAOH was a good marker for cumulative morbidity after RC. We propose that DAOH should be a standard supplement for reporting surgical outcomes following RC for bladder cancer, which may facilitate better comparison of outcomes across treating institutions.

**Patient summary:** We studied complications after surgical removal of the bladder for bladder cancer. We assessed a novel patient-centred tool that more accurately describes the total burden of complications after surgery than traditional models.

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We found that patients with a high body mass index and coexisting chronic diseases had a higher risk of a complicated surgical course.

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## 1. Introduction

Radical cystectomy (RC) with pelvic lymph node dissection is a recommended curative treatment for muscle-invasive bladder cancer (BC) and selected cases of high-risk non-muscle-invasive BC [1]. The procedure is associated with a high risk of short-term morbidity and a long recovery time [2–4]. To promote uniform reporting, the European Association of Urology (EAU) has recommended quality criteria for comprehensive reporting of outcomes after surgery [5]. The guideline recommends reporting of intra- and postoperative complications, readmissions, reoperations, and mortality data. These outcome measures of morbidity have been criticised for not providing any direct information on the patient experience. Morbidity is a result of both the quality and quantity of complications. Recently, days alive and out of hospital (DAOH) was proposed as a pragmatic measure of the combination of mortality, length of stay (LOS), and readmissions, integrating the elements expected to be of importance to patients. DAOH has been validated in a study of mixed surgical patients and its use in surgical series is increasing [6–8]. To the best of our knowledge, no procedure-specific data on DAOH after RC exist.

The objective of this study was to describe short-term morbidity, LOS, and DAOH in a contemporary cohort of patients who underwent RC using EAU criteria for reporting surgical morbidity.

## 2. Patients and methods

### 2.1. Patients

All patients who underwent RC for BC at the Department of Urology, Rigshospitalet, Denmark, between December 2009 and June 2019 were included. The period was chosen as the national electronic medical record (EMR) was available for all patients and the ongoing BORARC trial was initiated hereafter at our site [9]. Rigshospitalet is one of five tertiary referral centres for RC in Denmark. The indication for RC was muscle-invasive BC and selected high-risk non-muscle-invasive BC cases in accordance with the European guidelines [10].

### 2.2. Operative technique

The RC procedure included removal of the bladder and internal genitalia and pelvic lymph node dissection with the aortic bifurcation as the upper limit. RC was performed either as an open procedure or a robot-assisted laparoscopic procedure (RARC) since 2012, with urinary diversion performed intracorporeally since September 2015. The procedure used was chosen according to patient preferences and surgeon availability. During the study period, one surgeon performed all RARC procedures and a total of four different surgeons performed ORC.

### 2.3. Data

Data were collected retrospectively in the national EMR, which contains electronic patient charts from all hospitals in Denmark, including complete information on visits to emergency rooms, outpatient consultations, admissions, and vital status (including date of death) within 90 d after surgery. No patients were lost to follow-up. Data collection was carried out by a resident in urology (S.L.M.) who was not involved in the patient treatment.

The general health condition of the patient was appraised in terms of the CCI without age adjustment, as our aim was to describe CCI and the effect on short-term morbidity [11].

Complications within 90 d of surgery were recorded and graded according to the Clavien-Dindo classification (CDC) [12]. CDC grades I–II and IIIa–V complications were defined as minor and major complications, respectively. Recorded complications were stratified into ten categories according to the type or organ system affected (Supplementary Table 1). A complication was defined as any deviation from the optimal postoperative course. Any unscheduled contact with our department, outpatient clinic, or any other health care facility was categorised as at least a grade I complication. In the case of a complication occurring as a consequence of a prior complication, only the most severe complication was recorded, as suggested by Clavien et al [13]. Mortality was defined as death from any cause within 90 days of surgery.

Reoperation was defined as any procedure performed under general anaesthesia within 90 d of RC (eg, CDC grade IIIb). We included all operations performed within 90 d as reoperations, regardless of whether they related directly to the primary RC surgery.

Recovery after surgery was assessed using LOS and DAOH. LOS was calculated from the date of surgery to the date of discharge, including transfers to other departments. DAOH was calculated as:  $90 - (\text{LOS} + \text{length of any readmission} + \text{days dead before postoperative day 90})$ . Length of readmission was calculated from the date of readmission to the date of discharge. Patients readmitted and discharged on the same date were regarded as having a length of readmission of 1 d. Days dead before postoperative day 90 was calculated as the date of postoperative day 90 minus the date of death.

### 2.4. Outcomes

The primary outcome of our study was the 90-d postoperative major complication rate, LOS, and DAOH. We investigated intraoperative and overall complication rates, the frequency of complication types and categories, the readmission rate, and the reoperation rate as secondary outcomes. Furthermore, we aimed to identify predictors of a major complication, LOS, and DAOH.

The quality criteria for accurate and comprehensive reporting of surgical outcomes recommended by the EAU guidelines on reporting and grading of complications were fulfilled [5].

### 2.5. Statistical analysis

Multivariate logistic regression analyses were used to evaluate variables associated with a major complication, LOS >7 d, and DAOH <80 d.

**Table 1 – Patient characteristics**

| Parameter   | Result           |
|---|------------------|
| <b>Clinical preoperative characteristics</b>  |                  |
| Median age, yr (IQR)  | 68 (61–72)       |
| Males, n (%)  | 542 (74)         |
| Median body mass index, kg/m <sup>2</sup> (IQR) <sup>a</sup>  | 25.6 (23.3–28.7) |
| Smoking status, n (%) <sup>a</sup>  |                  |
| Never   | 134 (18)         |
| Ever  | 587 (81)         |
| American Society of Anesthesiologists score, n (%)  |                  |
| I   | 95 (13)          |
| II  | 442 (61)         |
| ≥III  | 192 (27)         |
| Charlson comorbidity index, n (%)   |                  |
| 0   | 279 (38)         |
| 1   | 234 (32)         |
| 2   | 131 (18)         |
| ≥3  | 85 (12)          |
| Median preoperative haemoglobin, mmol/l (IQR)   | 8.2 (7.4–8.9)    |
| Median preoperative eGFR, ml/min (IQR)  | 60 (47–82)       |
| Prior abdominal or pelvic surgery, n (%)  | 197 (27)         |
| Preoperative chemotherapy, n (%)  |                  |
| Neoadjuvant chemotherapy <sup>b</sup>   | 116 (16)         |
| Downstaging chemotherapy <sup>c</sup>   | 34 (4.7)         |
| Previous pelvic radiation therapy, n (%)  | 34 (4.7)         |
| <b>Perioperative characteristics</b>  |                  |
| Median operative time, min (IQR) <sup>a</sup>   | 224 (168–307)    |
| Median estimated blood loss, ml (IQR) <sup>a</sup>  | 940 (500–1423)   |
| Surgical technique, n (%)   |                  |
| Robot-assisted laparoscopic RC  | 152 (21)         |
| Open RC   | 567 (78)         |
| Lymph node dissection, n (%)  | 694 (95)         |
| Nerve-sparing RC, n (%)   | 20 (2.7)         |
| Concomitant nephroureterectomy, n (%) <sup>d</sup>  | 31 (4.5)         |
| Concomitant urethrectomy, n (%) <sup>e</sup>  | 204 (28)         |
| Urinary diversion, n (%)  |                  |
| Ileal conduit   | 586 (80)         |
| Orthotopic neobladder   | 78 (11)          |
| Continent cutaneous reservoir   | 40 (5.5)         |
| Other   | 24 (3.3)         |
| <b>Pathological characteristics</b>   |                  |
| pT stage (highest of TURB and RC), n (%) <sup>a</sup>   |                  |
| pTa   | 1 (0.14)         |
| pTis  | 31 (4.3)         |
| pT1   | 194 (27)         |
| pT2   | 260 (36)         |
| pT3   | 180 (25)         |
| pT4   | 60 (8.2)         |
| pTx   | 2 (0.27)         |
| pN+ stage, n (%) <sup>a</sup>   | 152 (21)         |
| pM1 stage, n (%) <sup>a</sup>   | 3 (0.41)         |
| Median number of lymph nodes removed, n (range)   | 17 (0–83)        |
| <p>eGFR = estimated glomerular filtration rate; IQR = interquartile range; TURB = transurethral resection of the bladder; RC = radical cystectomy.</p> <p><sup>a</sup> Missing data: body mass index, n = 79 (11%); smoking status, n = 6 (1.0%); operative time, n = 510 (70%); estimated blood loss, n = 189 (26%); pT stage, n = 1 (0.13%); pN+ stage, n = 1 (0.13%); pM1 stage, n = 1 (0.13%).</p> <p><sup>b</sup> From January 2013, all patients aged &lt;75 yr with ≥T2 stage disease, performance score 0–1, GFR ≥60 ml/min, and the absence of reduced liver function, peripheral neuropathy, and hearing disability were offered neoadjuvant chemotherapy (a standard of four cycles of gemcitabine plus cisplatin).</p> <p><sup>c</sup> In cases of locally advanced disease, patients were referred for downstaging chemotherapy (a standard of six cycles of gemcitabine plus cisplatin) before RC.</p> <p><sup>d</sup> A concomitant nephroureterectomy was performed in cases of a nonfunctional kidney or tumour in the upper urinary tract.</p> <p><sup>e</sup> A urethrectomy was performed immediately in cases of carcinoma in situ or malignancy in the urethra on perioperative frozen section pathological examination of the urethral margin.</p> |                  |

Logistic regression was chosen for analysis of LOS and DAOH as they have a complex distribution (skewed and highly skewed with a second small peak at 0 d, respectively), necessitating dichotomisation of these variables. Transformation of both LOS and DAOH was explored for linear regression modelling, but this was not possible. The cutoffs of 7 d for LOS and 80 d for DAOH were chosen empirically, as no data to substantiate any specific cutoffs were found for cystectomy patients in previous studies. A detailed description of the multivariable logistic regression analyses is outlined in the Supplementary material.

Statistical analysis was carried out using IBM SPSS Statistics version 25 (IBM Corporation, Armonk, NY, USA). A *p* value <0.05 was considered the threshold for statistical significance.

This study was approved by the Danish Patient Safety Authority (3-3013-2590/1) and data collection and handling were approved by the Danish Data Protection Agency (P-2019-204).

### 3. Results

A total of 729 patients were included. Clinical characteristics and perioperative and pathological outcomes are summarised in Table 1. No differences in preoperative parameters were found between the ORC and RARC groups (data not shown).

#### 3.1. Complications

Overall, 583 patients (80%) experienced an intra- or postoperative complication within 90 d after RC, as outlined in Supplementary Tables 1 and 2. A total of 115 patients (16%) had an intraoperative complication and 580 (80%) had one or more postoperative complications.

A total of 1357 postoperative complications were recorded among the 729 patients. The median number of complications experienced per patient was 1 (interquartile range (IQR) 1–3). A minor complication was experienced by 523 patients (72%), and 268 patients (37%) experienced a major complication. The distribution of the highest complication according to CDC grade was 10% for grade I, 33% for grade II, 10% for grade IIIa, 19% for grade IIIb, 3.2% for grade IVa, 2.1% for grade IVb, and 2.7% for grade V.

The most common complications were infectious (31%) and gastrointestinal (21%) complications, as outlined in Supplementary Table 1.

#### 3.2. Predictors of postoperative major complications

In multivariate regression analysis, a one-unit increase in body mass index (BMI) was significantly associated with a higher risk of a major complication (odds ratio (OR) 1.04, 95% confidence interval (CI) 1.00–1.08; *p* = 0.04). Patients with BMI >30 kg/m<sup>2</sup> had an OR of 1.60 (95% CI 1.02–2.53, *p* = 0.04) compared to patients with BMI of 18.5–25.0 kg/m<sup>2</sup>. Also, CCI was significantly associated with the risk of a major complication (OR 1.75, 95% CI 1.10–2.79; *p* = 0.02 for CCI = 2, and OR 2.22, 95% CI 1.30–3.81; *p* < 0.01 for CCI ≥3, compared to CCI = 0). RARC was associated with a lower risk of complications (OR 0.58, 95% CI 0.38–0.87; *p* = 0.01) compared to ORC. Age and tumour stage were not associated with the risk of complications (Supplementary Table 5).

**Table 2 – LOS, DAOH, and complication rates according to the year of surgery**

| Year | Patients, n | Median LOS, d (IQR) | Median DAOH, d (IQR) | Complication rate (%) |      |
|------|-------------|---------------------|----------------------|-----------------------|------|
|      |             |                     |                      | Major                 | Any  |
| 2009 | 7           | 9 (8–36)            | 76 (51–82)           | 42.9                  | 85.7 |
| 2010 | 59          | 8 (8–10)            | 80 (66–82)           | 37.3                  | 71.2 |
| 2011 | 64          | 8 (7–10)            | 80 (70–82)           | 39.1                  | 75.0 |
| 2012 | 67          | 9 (7–12)            | 80 (67–82)           | 38.8                  | 85.1 |
| 2013 | 78          | 8 (7–11)            | 79 (69–82)           | 43.6                  | 82.1 |
| 2014 | 94          | 7 (6–9)             | 82 (76–83)           | 28.7                  | 71.3 |
| 2015 | 79          | 7 (5–8)             | 80 (73–84)           | 41.8                  | 81.0 |
| 2016 | 76          | 6 (4–10)            | 80 (73–84)           | 36.8                  | 81.6 |
| 2017 | 84          | 5 (3–9)             | 81 (72–84)           | 33.3                  | 86.9 |
| 2018 | 73          | 6 (3–8)             | 80 (71–85)           | 39.7                  | 82.2 |
| 2019 | 48          | 5 (4–8)             | 83 (71–85)           | 25.0                  | 77.1 |

LOS = length of stay; DAOH = days alive and out of hospital; IQR = interquartile range.

### 3.3. Recovery

Median LOS was 7 d (IQR 6–9) and median DAOH was 80 d (IQR 71–83) in our cohort. The median LOS decreased from 9 d in 2009 to 5 d in 2019, while DAOH increased from 79 to 83 d in the same period. Median LOS and DAOH results for every year are outlined in [Table 2](#).

The occurrence of a major complication was significantly associated with both LOS >7 d ( $p < 0.001$ ) and DAOH <80 d ( $p < 0.001$ ). [Figure 1](#) shows the association between the highest complication experienced per patient and LOS and DAOH.

In addition, CCI = 2 (OR 1.79, 95% CI 1.14–2.80,  $p = 0.01$ ) and CCI  $\geq 3$  (OR 1.90, 95% CI 1.12–3.23;  $p = 0.02$ ) were significantly associated with LOS >7 d when compared to CCI = 0. Patients with CCI  $\geq 3$  had significantly higher odds of having DAOH <80 d compared to those with CCI = 0 (OR 1.81, 95% CI 1.06–3.08,  $p = 0.03$ ).

LOS decreased and DAOH increased over the years for both ORC and RARC, with no significant differences between the two surgical methods (Supplementary Fig. 1). However, in multivariable logistic regression analyses, RARC was associated with lower odds of LOS >7 d (OR 0.37, 95% CI 0.25–0.55;  $p < 0.001$ ) and DAOH <80 d (OR 0.52, 95% CI 0.35–0.76;  $p < 0.01$ ) when compared to ORC (Supplementary Tables 6 and 7).

### 3.4. Reoperations

A reoperation was performed in 22% of the patients. The most frequent reason for reoperation was fascial dehiscence (8.4%). All indications for reoperations are listed in Supplementary Table 3.

### 3.5. Readmissions

A total of 345 patients (47%) were readmitted at least once within 90 d after RC. The most frequent cause of readmission was infectious complications (47%). All reasons for readmission are listed in Supplementary Table 4.

### 3.6. Mortality

A total of 20 patients (2.7%) died within 90 d after RC. Causes of death included pulmonary aspiration ( $n = 4$ ), gastrointestinal perforation ( $n = 2$ ), anastomotic bowel leak ( $n = 1$ ), sepsis ( $n = 3$ ), gastroenteritis ( $n = 1$ ), unexpected cardiac arrest ( $n = 2$ ), pneumonia ( $n = 1$ ), ruptured aortic abdominal aneurysm ( $n = 1$ ), and progression of malignant disease ( $n = 2$ ); three patients died out of hospital with unknown cause of death.

## 4. Discussion

Our aim was to comprehensively describe short-term morbidity and recovery after RC in a contemporary cohort, applying current EAU guidelines on reporting of complications.

Our study is the first to report on DAOH in a cohort of RC patients. We report a median 90-d DAOH of 80 d and identified comorbidity as a predictor of a DAOH <80 d. Patients with CCI  $\geq 3$  had a 81% higher risk of DAOH <80 d compared to those with CCI = 0. LOS has been the outcome measure of recovery after RC most commonly used in the literature, with median LOS ranging from 5 to 24 d [4,14]. However, LOS does not cover events encountered after the index hospitalisation. As a proxy for recovery, DAOH captures both the number and severity of events, as both mortality and hospitalisation duration are part of this compound variable (illustrated in [Fig. 1](#)). In our cohort, median LOS was 7 d, with a decrease from 9 to 5 d observed over the study period. It has consistently been shown that enhanced recovery after surgery (ERAS) protocols reduce LOS, and gradual implementation of ERAS principles in our perioperative care over the study period is the likely explanation for this decrease [15,16]. Median DAOH increased by 4 d over the study period, reflecting that ERAS protocols reduce the duration of the index hospitalisation, but have limited effects on the postoperative course over the first 3 mo. This finding was observed for both ORC and RARC (Supplementary Fig. 1). We did not observe changes in patient age, tumour stage, or CCI over

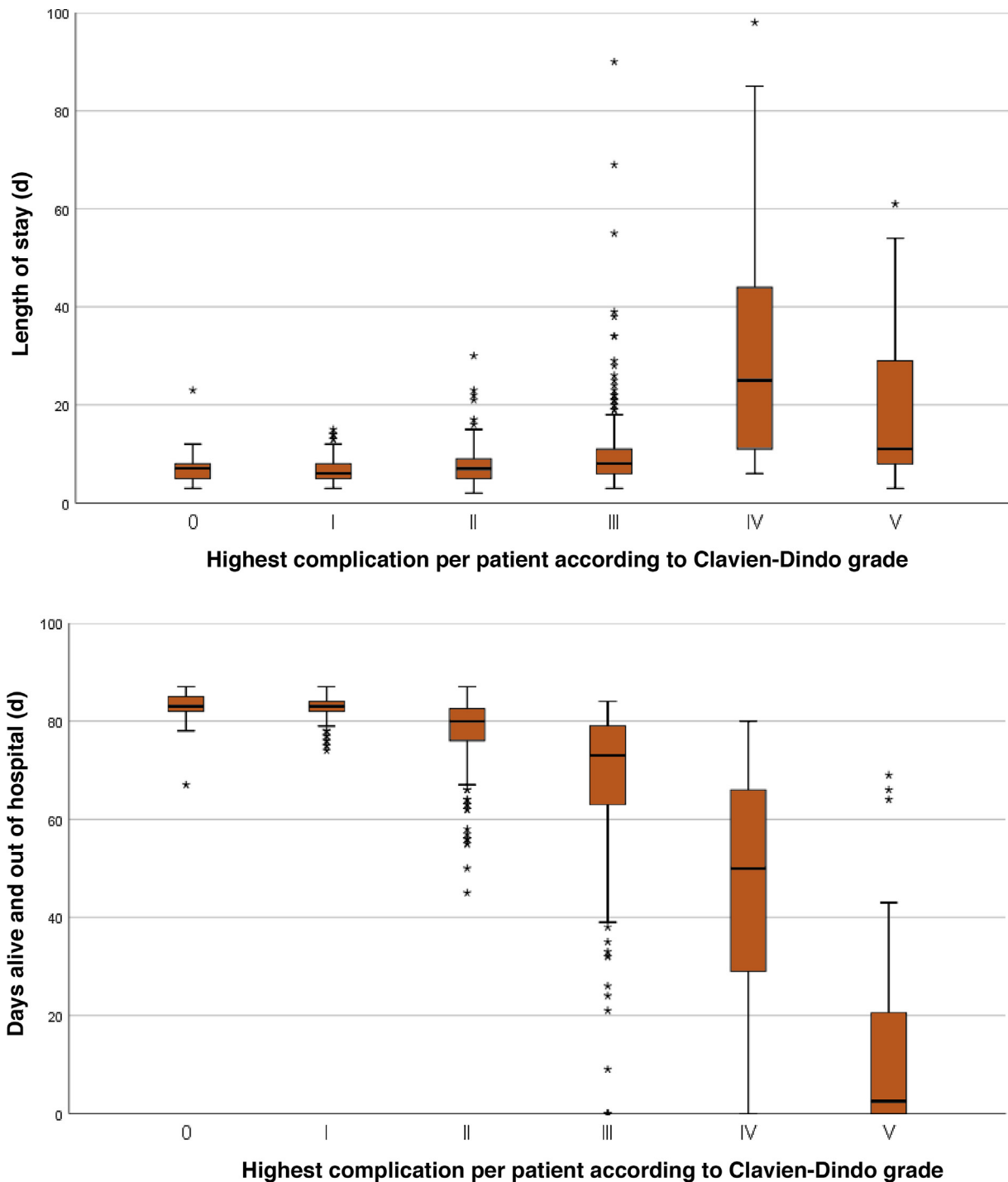


Fig. 1 – Days alive and out of hospital and length of stay according to the highest complication experienced per patient.

the study period (data not shown), or in the rate of major complications.

We believe that DAOH can be used as an objective measure of recovery and an indicator of quality following RC. We advocate that DAOH should replace LOS as an outcome measure, as recovery extends beyond the index hospitalisation. Previous studies reporting complication rates at several postoperative time points have shown that

the complication rate increases substantially from the index hospitalisation to 30 d postoperatively, and even though it still increases from 30 to 90 d postoperatively, this increase is not as marked [2,17–19]. Therefore, DAOH should be measured within at least 30 d and preferably 90 d after RC.

RC is a complex major surgical procedure associated with high morbidity. Quantification of morbidity has been diverse, and therefore the EAU has proposed quality criteria for



standardised reporting to make comparison across series easier. To the best of our knowledge, only a few other studies have fulfilled these criteria after RC [20–22]. In accordance with the results of the PURE-01 trial, we found that a major complication occurred in approximately one-third of all patients undergoing RC. The PURE-01 trial reported a major complication rate of 34% and an overall 90-d complication rate of 77% [22]. Although our cohort may not be directly comparable to the PURE-01 trial, our findings seem similar. On the contrary, Vetterlein et al [20] reported a 30-d rate of severe complications (CDC grade  $\geq$ IIIb) of 11%, but an overall 30-d complication rate of 99%. In comparison, our 90-d severe complication rate was 27% and our 30-d overall complication rate was 73% (data not shown). Mazzone et al [21] did not report the rate of major or overall complications, but a 30-d rate of CDC grade  $\geq$ 2 complications of 38%. The most likely explanation for these differences is related to the definition of a complication. In contrast to our study, Vetterlein et al [20] defined asymptomatic bacteriuria and hydronephrosis as CDC grade I. In our cohort, asymptomatic bacteriuria and hydronephrosis were not defined as complications if not treated, as these can be normal findings in patients after RC. In addition, haematuria was frequent in their study, occurring in 67% of patients [20]. Haematuria can occur in the first postoperative days and is not necessarily documented on the patient chart if no intervention was needed. Grading of complications can also differ even when using the same classification system, as grading can be subject to interpretation. Vetterlein et al [20] considered constipation and diarrhoea treated with laxatives and antidiarrhoea agents, respectively, as CDC grade I. We graded these complications as CDC grade II, as these drugs are not mentioned as “permitted” for the CDC grade I category [12]. In addition, placement of a catheter for urinary retention was categorised as CDC grade I, whereas we categorised this as a grade II complication. However, it is not always outlined in detail how complications are defined and categorised. For example, neither Briganti et al [22] nor Mazzone et al [21] reported any cases of urinary retention (and subsequent placement of a catheter) as a complication, although 46% of the patients in the study by Briganti et al [22] received a neobladder. It is debatable whether all minor deviations from the standard postoperative course should be considered as complication, as they do not necessarily significantly impact the postoperative course or prolong recovery.

Interestingly, we found that ORC was associated with longer LOS, fewer DAOH, and experiencing a major complication compared to RARC. The association between shorter LOS and a lower complication rate with RARC has been established in several previous retrospective studies [23–26]. However, these findings have not been proven in any randomised controlled trial [27–31]. Despite the adjustment for explanatory variables in the multivariable regression analyses, selection is most likely the explanation for this finding, as, for example, ORC was more frequently performed for patients with previous abdominal/pelvic surgery. DAOH is currently being investigated as an outcome in the ongoing randomised iROC trial comparing ORC and RARC with intracorporeal urinary diversion [32].

The present study has limitations. The retrospective nature of the study could potentially lead to underestimation of minor complications (especially CDC grade I) since these may not have been detailed in the EMR. Second, the lack of two independent assessors of complication registration and grading from the EMR can be perceived as a study weakness. However, in a survey among 2016 surgeons with different levels of expertise, 90% of the respondents provided an accurate classification, indicating low interobserver variability [12]. Third, our investigation covers a 10-yr time interval. Changes in pre-, intra-, and postoperative patient management have occurred over the past decade, which might in part limit the applicability of these findings to contemporary patients. Lastly, we anticipate that higher DAOH is associated with higher quality of life, but data were not available for this study. Strengths of the current study include a large cohort with a high level of granularity of data owing to the meticulous manual search of every patient’s EMR, including access to the electronic national patient chart to retrieve complete information on all readmissions and procedures in all hospitals in Denmark. This largely eliminates the risk of under-reporting of major complications including deaths, and there was no loss to follow-up.

## 5. Conclusions

This study reaffirms that RC is associated with high short-term morbidity. Our study is the first to report DAOH after RC and demonstrated that median DAOH was 80 d. DAOH is associated with prolonged LOS, number of readmissions, and major complications capturing the cumulative morbidity after RC. This underlines the fact that the postoperative recovery period is not restricted to the index hospitalisation and we suggest that DAOH should replace LOS as an outcome measure of recovery.

**Author contributions:** Sophia L. Maibom 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:** Maibom, Røder, Thind, L.N. Salling, Kehlet, Brasso, Joensen.

**Acquisition of data:** Maibom, Poulsen, Thind, M.L. Salling.

**Analysis and interpretation of data:** Maibom, Røder, Joensen.

**Drafting of the manuscript:** Maibom.

**Critical revision of the manuscript for important intellectual content:** All authors.

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## CRedit authorship contribution statement

**Sophia L. Maibom:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Martin A. Røder:** Conceptualization, Methodology, Supervision, Writing - review & editing. **Alicia M. Poulsen:** Investigation, Writing - review & editing. **Peter O. Thind:** Conceptualization, Writing - review & editing. **Marie L. Salling:** Investigation, Writing - review & editing. **Lisbeth N. Salling:** Conceptualization, Writing - review & editing. **Henrik Kehlet:** Conceptualization, Supervision, Writing - review & editing. **Klaus Brasso:** Conceptualization, Supervision, Writing - review & editing. **Ulla N. Joensen:** Conceptualization, Methodology, Supervision, Writing - review & editing.

## 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.euros.2021.03.010>.

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