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RESEARCH ARTICLE

Predictors of Major Complications and the Association with Oncological Outcomes After Radical Cystectomy for Bladder Cancer: A Nationwide Registry Study

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ABSTRACT

Introduction Radical cystectomy improves survival of patients with muscle invasive and high-risk non-muscle invasive bladder cancer, but is a challenging surgical procedure as patients may experience major complications after surgery.

Objectives To assess the incidence of Clavien-Dindo ≥3 complications in patients who underwent radical cystectomy and to assess the association of these complications with pre-operative and peroperative parameters. The secondary aim was to study the association of complications with long-term oncological outcome.

Methods A nationwide registry was set up in 19 Dutch hospitals that studied patients with muscle invasive bladder cancer and high-risk non-muscle invasive bladder cancer treated by radical cystectomy. Major complications were classified as complications that were related to uretero-ileal anastomosis, intra-abdominal (e.g. urinoma, bowel leakage) infectious and cardiovascular complications. Multivariable logistic regression analyses were performed to assess the correlation between these groups and perioperative, clinical and pathological factors. Kaplan-Meier survival curves were constructed to analyze the correlation between complications and overall survival.

Results The study population consisted of 1,464 patients, of whom 420 (29%) developed severe complications. The most common complications were intra-abdominal (n=328, 60%) and uretero-ileal anastomosis related (n=92, 17%). Male gender (odds ratio 1.6, p=0.007), American Society of Anaesthesiologists score ≥3 (odds ratio 1.6, p=0.003), Charlson Comorbidity Index score ≥5 (odds ratio 2.1, p=0.002) and blood loss >700ml (odds ratio 1.4, p=0.044) were associated with severe complications. In addition, open radical cystectomy was associated with multiple complications (odds ratio 2.6, p=0.001). Furthermore, the overall survival of patients with major complications was worse than those who had no major complications. The median overall survival was 3.8 years versus 6.2 years for patients with and without severe complications (p<0.001).

Conclusions In a real-world setting, 29% of patients undergoing radical cystectomy developed severe complications. The risk of severe complications was higher in men, patients with impaired pre-operative condition, and in those who underwent open surgery. Severe complications had a negative impact on overall survival.

Keywords: complications, muscle invasive bladder cancer, radical cystectomy

1. Introduction

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is advised in patients with muscle invasive bladder (MIBC) or (very) high-risk non-muscle invasive disease (NMIBC).[1] This surgical procedure has demonstrated oncological benefits in the long-term, although it is associated with a high incidence of complications, including hospital mortality within 30 or 90 days postoperatively.[2-5] Immediate post-operative complications may involve postoperative gastroparesis and ileus, (considerable) blood loss, thrombo-embolic events, urinary leakage, as well as abdominal or wound infections.[2-5] Kidney function loss and uretero-ileal anastomotic (UIA) stricture are possible late post-operative complications.[6]

Several patient and procedural factors may influence the risk of complications following RC. For instance, patients with pre-existing medical conditions, such as cardiovascular disease or diabetes mellitus, may be at higher risk of developing complications.[7] Additionally, the surgical approach might influence the complication rate. The classic method for performing RC is the open radical cystectomy (ORC). However in recent years, alternative surgical approaches have emerged, such as laparoscopy (LRC) or robot-assisted radical cystectomy (RARC). These minimally invasive procedures have shown potential benefits including reduced blood loss, decreased postoperative pain and shorter recovery time.[1,4] Several randomised controlled trials (RCTs) demonstrated equal risk of complications in ORC versus RARC with similar oncological outcomes.[3,8,9]

Despite advances in surgical techniques and perioperative care, evidence on what factors influence complication rates is mixed due to differences in study populations and outcome measures across studies. Therefore, we conducted a multicentre observational study using data from a large national population-based registry of patients with MIBC and high-risk NMIBC who underwent RC. We primarily studied the association between perioperative parameters and the development of complications Clavien-Dindo grade 3 and higher. Secondly, we studied the association between the prevalence of major complications and long-term oncological outcome.

2. Patients and methods

2.1 Data acquisition

The Dutch Cystectomy Snapshot study (DCSs) is a retrospective, multicenter observational cohort study that aims to report on the intermediate-term survival of patients with MIBC who underwent radical surgery.[10] The participating hospitals were not selected based on hospital-volume or patient criteria, to ensure that the study results are generalizable to routine clinical care. In total, 19 out of 47 (40%) hospitals in The Netherlands that performed RC participated in the DCSs, including five university and fourteen general hospitals. The study included data from 1,604 patients with non-metastatic MIBC or high-risk NMIBC who underwent RC between January 2012 and December 2015.[10] In cases where clinical and pathological disease stage or the vital status of the patient's data was missing, information was supplemented by data obtained from the Netherlands Cancer Registry (NCR), a comprehensive nationwide network that registers all cancer patients based on the histology and cytopathology registry in the Netherlands (in Dutch: PALGA www.palga.nl).

2.2 Clinical, perioperative and pathological parameters

The present study retrospectively collected the following clinical data from patient charts (Table 1): age (years), gender (male, female), body mass index (BMI, kg/m^2), previous major abdominal surgery (yes or no, i. e. low anterior resection, right hemicolectomy, open vascular surgery), Charlson comorbidity index (CCI, categorized in 0-2, 3-4 or >5 points), American Society of Anesthesiologists (ASA)-score (1-4 points), pre-operative estimated glomerular filtration rate (eGFR, µmol/L) and hemoglobin (Hb, mmol/L). Furthermore, outcome parameters related to treatment were evaluated, including the use of neo-adjuvant chemotherapy (none, chemotherapy, radiotherapy, other), the surgical approach (open, laparoscopically or robot-assisted), the type of urinary deviation (neo-bladder or uretero-ileal-cutaneostomy), the extent of pelvic lymph node dissection (more or less than 15 lymph nodes), any concurrent surgery (yes or no, i.e. nephrectomy, colectomy, anterior pelvic exenteration, or prostatectomy), surgery time (minutes), length of hospital stay (days), estimated blood loss (mL). Additionally, tumor characteristics were determined according to the TNM-classification [11], such as clinical (cT) and pathological (pT) tumor stage (T1/cis, T2, T3, T4) as well as clinical and pathological lymph node stage (cN and pN, respectively, N0, N1, N2).

2.3 Postoperative complications

The national registry contained data on postoperative major complications and postoperative 30-days and 90-days mortality. Complications were rated according to the Clavien-Dindo classification.[12] In this classification, grade 1-2 are graded as minor complications and grades 3-

5 are assessed as major as they require surgical, endoscopic or radiological intervention (3a), intervention under general anesthesia (3b), intensive care (4) or result in death (5).[12] Due to numerous specific complications and therefore small sample sizes for analysis, the complications were assigned to groups: complications related to uretero-ileal anastomosis (UIA, including urine leakage, necrosis or dehiscence of stoma and hydronephrosis due to ureteral obstruction), abdominal complications (including wound dehiscence, intestinal necrosis or infarction, ileus, intestinal anastomotic leakage, postoperative haemorrhage, abscess or (infected) lymphocele), cardiovascular complications (including thromboembolic events, myocardial infarction, cerebrovascular events and miscellaneous cardiovascular events) and infectious complications (urinary tract infection, non-urinary tract related, wound infection and location unknown or sepsis).

2.4 Outcomes

We examined the correlation between clinical, perioperative and pathological factors and the incidence of major postoperative complications according to Clavien-Dindo. In addition, we evaluated the association between the development of major postoperative complications (Clavien-Dindo classification ≥3a) at 90 days and long-term overall survival (OS) following RC.

2.5 Statistical analysis

The statistical analyses were performed using IBM® SPSS® Statistics version 25. All demographic and clinical variables were reported with percentiles in case of categorical variables and median with interquartile range in case of continuous variables. Multivariable logistic regression analyses were performed to assess the association between patient characteristics or surgical factors and complication rate. Continuous variables were categorized. Results were reported in odds ratio (OR) and 95% confidence intervals (95%CI). Further, Kaplan-Meier survival curves were used to analyze the correlation between complications and OS since hospital discharge. Patients who were lost to follow-up were censored at the last date of recorded follow-up. The threshold for statistical significance was held at $p<0.05$.

3. Results

3.1 Population

The study population consisted of a total 1,604 patients with high-risk NMIBC and MIBC who underwent RC with urinary diversion. The median follow-up was 3.7 years. Patients who underwent non-standard concurrent surgeries such as nephrectomy or enterectomy (including duodenectomy, low anterior resection and colectomy) were excluded from analysis (n=139). Patients who simultaneously underwent anterior pelvic exenteration or prostatectomy were included in the analysis. This led to a total of 1,464 patients who were analyzed. Of these patients, 86 (6%) underwent LRC, 998 (68%) underwent ORC and 380 (26%) underwent RARC. Clinical patient characteristics and surgical parameters are listed in Table 1. The most common urinary diversion was the ileal conduit (1,236 patients, 85%), followed by the orthotopic bladder (184 patients, 13%).

Table 1 Clinical and perioperative characteristics of 1,464 patients with bladder cancer who underwent radical cystectomy.

Variable	n	%	Median (IQR)	Missing
Age (years)			68 (62-74)	
Male gender	1,107	76		
Body Mass Index (kg/m2)			26 (23-28)	
Previous abdominal surgery	136	9		12
CCI				
0-2	383	26		
3-4	606	42		
≥5	463	32		
ASA				103
1	252	19		
2	843	62		
≥3	266	20		
Clinical tumor stage (7th ed., cT-stage)				26
cT1/cis	285	20		
cT2	748	52		
cT3	330	23		
cT4	75	5		
Clinical nodal stage (7th ed., cN-stage)				36
cN0	1,299	91		

cN1	97	7		
cN2	32	2		
Pre-operative eGFR			72 (57-86)	
Pre-operative hemoglobin (mmol/L)			8 (7-9)	
Neo-adjuvant therapy				10
None	1107	76		
Chemotherapy	333	23		
Radiotherapy	8	1		
Other	6	0		
Type of surgery				
ORC	998	68		
LRC	86	6		
RARC	380	26		
Type of urinary deviation				*7*
Ileal conduit	1,236	85		
Continent Pouch	31	2		
Orthotope bladder	184	13		
Other	3	0		
Ureterocutaneostomy	3	0		
Duration of surgery (minutes)			280 (230-346)	
Estimated blood loss (mL)			700 (400-1,300)	

IQR = interquartile range; CCI = Charlson Comorbidity score; ASA = American Society of Anaesthesiologists score; eGFR = estimated glomerular filtration rate; ORC = open radical cystectomy; LRC = laparoscopic radical cystectomy; RARC = robot assisted radical cystectomy;

3.2 Complications

The majority of patients did not experience major complications (n=1,027, 71%), as depicted by Table 2. The major complications that occurred most commonly were grade 3a (170, 33%) and grade 3b (226, 43%). Grade 4 and 5 complications were less common, namely 90 (18%) and 35 (7%) times. Of the 420 patients who had a major complication postoperatively, 122 (8%) patients experienced more than 1 major complication and data on 17 patients was missing. The most common complication types were abdominal complications (328, 60%) and UIA-related complications (92, 17%). Infections occurred 89 (16%) times and cardiovascular complications occurred 42 (8%) times. Details are shown in Table 3.

Table 2 Major complications according to Clavien-Dindo of 1,464 patients with bladder cancer who underwent radical cystectomy

	n	%
Complications (per patient)		
Yes	420	29
Missing	17	
Any complication (per patient)		
0	1,027	71
1	298	21
>1	122	8
Missing	17	
Clavien-Dindo grades (per event)		
3a	170	33
3b	226	43
4a	71	14
4b	19	4
5	35	7
Missing	30	
Total amount of complications	551	

Table 3 Specifications of the complication groups and the 551 major complications that developed following radical cystectomy

Group	Components	Clavien-Dindo	Count	Total (%)
Uretero-intestinal anastomosis related complications	Ureteric anastomotic leakage	3	42	92 (17)
	Stoma necrosis or dehiscence	3	6	
	Hydronephrosis	3	44	
Abdominal complications	Wound dehiscence, necrosis or infarction	3	84	328 (60)
	Ileus	3	70	
	Bowel anastomic leakage or perforation	3	72	
	Intra-abdominal hemorrhage	3-5	17	
	Intra-abdominal abscess or lymphocele	3	85	
Cardiovascular complications	Thromboembolic event	3-5	8	42 (8)
	Myocardial infarction	3-5	10	
	Cerebro-vascular event	3-5	7	
	Miscellaneous cardiovascular events	3-5	17	
Infectious complications	Urinary tract infection	3-5	28	89 (16)
	Location unknown, sepsis	3-5	16	
	Not-urinary tract related	3-5	31	
	Wound infection	3	14	

3.3 Impact of clinical factors on major complications

Logistic regression analysis was performed for the association between postoperative major complications according to Clavien-Dindo and preoperative and perioperative clinical, pathological and parameters. Table 4 demonstrates that surgically treated men had a 1.6 times higher likelihood of developing a major complication than women (95%CI 1.1-2.3). Also, patients with an ASA score of three or higher were more likely to experience a major complication (OR 1.6 (95%CI 1.2-2.3). Similarly, patients with a CCI score of three or higher were also at a greater risk of developing major complications, with an OR of 1.8 (95%CI 1.1-2.6) for CCI of three or four and an OR of 2.1 for scores five or higher (95%CI 1.3-3.3). Furthermore, these patients were more likely to experience multiple complications: patients with the highest CCI and ASA scores had an OR of 3.0 (95%CI 1.3-6.7) and an OR of 2.3 (95%CI 1.5-3.7), respectively.

Interestingly, BMI was not associated with the development of major complications. However, if patients with a higher BMI had any complications, they were more likely to suffer from more than one: OR for patients with a BMI >30 was 2.5 (95%CI 1.3-4.6). Also noteworthy is that neo-adjuvant (chemo)therapy was not associated with the development of major complications and even lowered the likelihood of developing multiple complications: OR of 0.5 (95%CI 0.3-1.0). Further, older age, previous abdominal surgery, cT-status and cN-stage, preoperative Hb and eGFR values were not associated with the development of major complications.

Table 4 Multivariable logistic regression to assess the association between patient factors and the development of complications and development of multiple complications, n=1,464.

	Development of complications				**Development of multiple complications**			
	OR	95% CI		p-value	OR	95% CI		p-value
Age (years)								
<60	(reference)				(reference)			0.19
60-69	0.77	0.51	1.16	0.21	0.78	0.40	1.54	0.48
≥70	0.67	0.42	1.06	0.09	0.54	0.26	1.13	0.10
Body Mass Index (kg/m2)								
>25	(reference)			0.31	(reference)			0.01
25-30	1.11	0.82	1.49	0.51	1.97	1.16	3.35	0.01
>30	1.36	0.92	1.99	0.12	2.47	1.32	4.61	0.01
Gender								
Female	(reference)				(reference)			
Male	1.61	1.14	2.27	0.01	1.54	0.86	2.78	0.15
Previous abdominal surgery								
No	(reference)				(reference)			
Yes	0.74	0.47	1.17	0.19	1.29	0.58	2.86	0.53
Clinical Tumor stage (cT)								
cT-stage ≤cT2	(reference)				(reference)			
cT-stage ≥cT2	1.08	0.79	1.49	0.63	1.60	0.96	2.65	0.07
Clinical Nodal stage (cN)								
cN-stage cN0	(reference)				(reference)			
cN-stage cN+	0.93	0.57	1.53	0.78	1.56	0.72	3.38	0.26
CCI								
CCI 0-2	(reference)				(reference)			
CCI 3-4	1.71	1.14	2.56	0.01	2.76	1.33	5.74	0.01
CCI ≥5	2.10	1.32	3.34	0.00	3.01	1.34	6.73	0.01
ASA								
ASA ≤3	(reference)				(reference)			
ASA ≥3	1.64	1.18	2.27	0.00	2.33	1.45	3.74	<.001
Neo-adjuvant therapy								
No	(reference)				(reference)			
Yes	0.81	0.56	1.17	0.25	0.49	0.26	0.94	0.03
Pre-operative eGFR (µmol/L)								
eGFR ≥60	(reference)				(reference)			
eGFR<60	1.04	0.77	1.40	0.82	1.10	0.68	1.77	0.71
Pre-operative hemoglobin (mmol/L)								
Normal level	(reference)				(reference)			
Anemic	1.00	0.75	1.35	0.98	1.04	0.65	1.67	0.87

OR= odds ratio; 95%CI = 95% Confidence interval; CCI = Charlson Comorbidity score; ASA = American Society of Anaesthesiologists score.

3.4 Influence of perioperative factors on complications

Table 5 shows the results from a logistic regression analysis on the association of perioperative factors and major complications. The risk of complications was lower with RARC, while ORC was associated with multiple complications: OR 2.6 (95%CI 1.5-4.8). Noteworthy, clinical factors were not included in this model thereby not adjusting for patient selection. High estimated blood loss (≥700 mL) (OR 1.3, 95%CI 1.0-1.7) and long duration of surgery (≥280 minutes) (OR 1.3, 95%CI 1.0-1.7) were also associated with the development of complications.

Table 5 Multivariable logistic regression to assess the association between surgical factors and the development of complications and the development of multiple complications, n=1,464

	Development of complications				**Development of multiple complications**			
	OR	95% CI		p-value	OR	95% CI		p-value
Surgical approach								
RARC	(reference)				(reference)			
ORC	1.38	0.98	1.93	0.06	2.64	1.46	4.80	0.00
LRC	2.32	1.40	3.86	0.00	1.87	0.79	4.45	0.16
Urinary deviation								
Ileal conduit	(reference)				(reference)			
Other urinary deviation	0.93	0.66	1.31	0.66	1.00	0.59	1.70	0.99
Duration of surgery (minutes)								
<280 min	(reference)				(reference)			
≥280 min	1.31	1.01	1.70	0.04	1.00	1.00	1.01	<.001
Estimated blood loss (mL)								
<700 mL	(reference)				(reference)			
≥700 mL	1.42	1.07	1.88	0.02	0.90	0.57	1.41	0.63
Lymph node yield at dissection								
Low yield <15	(reference)				(reference)			
High yield ≥15	1.00	0.78	1.28	0.98	1.10	0.74	1.64	0.63

OR= odds ratio; 95%CI = 95% Confidence interval; ORC = open radical cystectomy; LRC = laparoscopic radical cystectomy; RARC = robot assisted radical cystectomy.

3.5 Influence of complications on survival

The Kaplan-Meier curve in figure 1 illustrates the OS of 1,426 patients from the time after discharge from hospital after RC for patients with major complications compared to those who have not experienced any major complications. The analysis revealed that patients who developed major postoperative complications had a significantly worse OS. Those who had at least one major complication had a median survival of 3.8 years (95%CI 2.9-4.6) compared to patients without any major postoperative complications, who had a median survival of 6.2 years (95%CI 5.7-6.7), p<0.001. Patients who had a single major complication had a median survival of 4.0 (95%CI 3.0-4.9) while those who had two or more major complications had a median survival of 3.1 years (95%CI 1.1-4.9), Log Rank test p<0.001 (figure not shown).

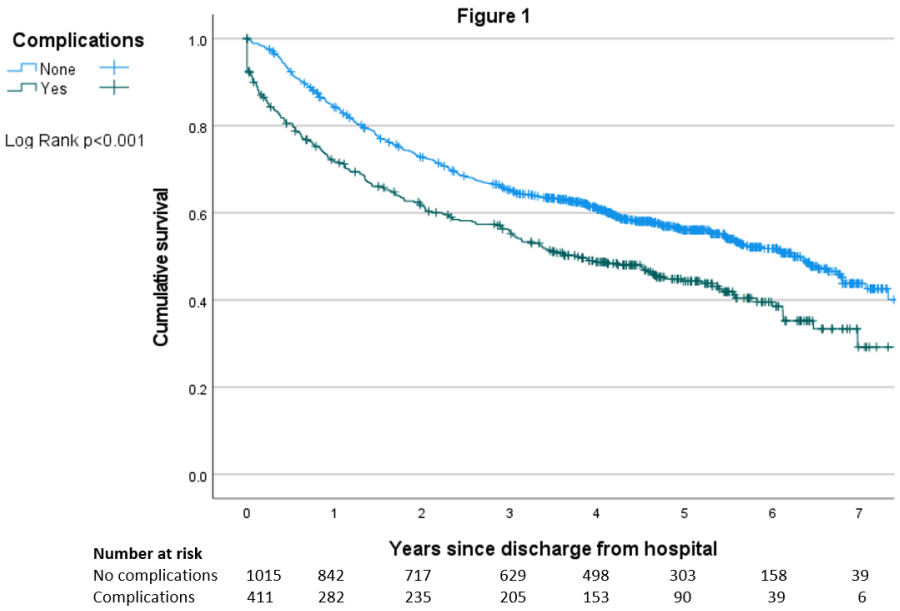

Figure 1. Kaplan-Meier curve of overall survival in 1,426 patients with muscle-invasive bladder cancer who were treated by RC. The blue curve shows the OS of patients who did not experience major complications according to Clavien-Dindo, the green curve shows that of patients who experienced at least one complication.

4. Discussion

In our multicentre, population-based cohort of 1,464 patients undergoing RC for bladder cancer, we found that more than a quarter of patients experienced major complications (Clavien-Dindo ≥3). Male gender, ASA score ≥3 and CCI score ≥3 were the preoperative clinical factors with an increased odds of suffering from a major complication. ORC, high estimated blood loss and longer duration of surgery were the perioperative factors with an increased odds of suffering from (multiple) major complications. Patients experiencing major complications had a statistically significant worse intermediate term overall survival. The major complication rate of 29% in our cohort is consistent with the rates reported in other population based studies, though these rates vary widely between 34% and 80%.[2,8,13,14]. Our complication rate is higher than what has been reported in RCT's, e.g. the RAZOR trial (22%) and the RACE study (16%).[3,8,15,16] However, these trials all have excluded patients based on severe comorbidity and previous abdominal surgery, whereas our study did not. Furthermore, it is important to acknowledge that randomized controlled trials (RCTs) may yield lower rates of major complications compared to observational studies due to inherent biases, such as the selective enrolment of patients with lower baseline risk factors, more stringent inclusion and exclusion criteria, and more standardized and closely monitored interventions. Therefore, caution should be exercised when comparing rates across different study designs and populations. Another important note is that these studies were often performed in high volume centres and that RARC is a complex procedure that requires skill and expertise. Studies have shown that the degree of proficiency and experience of the surgeon can have a significant impact on the rate of complications and outcomes for the patient.[17,18] As our study did not select hospitals based on volume, it provides a more diverse and inclusive sample, which better reflects the real-world practice.

In our cohort, patients undergoing ORC had higher odds for multiple major complications than patients undergoing RARC. According to the available literature, the complication rates seem similar for RARC and ORC. Both blood loss and duration of surgery have been identified as predictors of complications of any grade.[13,19] Lower blood loss is thought to be an advantage of RARC while a shorter duration of surgery is an advantage attributed to ORC.[2,20] Several recent RCTs link ORC with the development of wound-related complications but do not observe a general statistical difference between ORC and RARC.[2,16,20] A probable reason for the higher odds of multiple major complications after ORC is that we did not adjust for preoperative clinical factors. Moreover, in contrast with the aforementioned RCT's, we did not exclude patients with severe comorbidity and previous abdominal surgery who could be at higher risk of complication.

It is known from literature that poor pre-operative conditions including malnutrition, low albumin levels

and poor performance status are associated with the development of complications.[21-23] A systematic review on 81 studies concluded that the overall 90 day complication rate increased for every 1-unit increase in BMI.[21] Furthermore, the ASA and CCI score have been found to be a prognostic factor for (perioperative) mortality and can be used to estimate long-term survival.[1,24] Our findings and current literature on the association of complications and BMI, CCI and ASA scores underline the importance of a healthy baseline status prior to major surgery.[21,23-25] Several literature reviews have described that exercise interventions and perioperative nutritional optimization in cancer patients have positive effects, including improved physical performance and decreased risk of complications.[26-28] Despite increasing evidence, the current EAU guideline on MIBC provides no recommendations on diet or exercise based optimisation programs prior to RC.[1]

Our analysis showed a significant reduction of 2.4 years in the median survival in patients suffering from only one major complication after RC than those who experienced no major complications. Notably, this survival difference was found with the exclusion of direct post-operative mortality by solely including patients surviving the primary admission. Obviously, this finding can largely be contributed to selection bias. However, the Dutch Snapshot Cystectomy Study group has reported previously that suffering more than one severe complication during RC was linked to worse OS and that severe complications were associated with worse recurrence free survival.[10] A large population based analysis that stratified survival for complications after RC showed that experiencing complications results in increased predicted probability of mortality.[29] These findings underline the importance of early diagnosis and treatment of complications, but also that of prevention.

In an attempt to lower the complication rate, prediction models have been developed to improve patient selection for surgery.[24,29,30] However, these risk calculators often have poor accuracy at predicting postoperative morbidity and mortality.[31] Therefore, a multidisciplinary approach remains an important tool in perioperative care.

Limitations

Limitations of our study include those inherent to its observational and retrospective nature. In the multivariable and survival analyses there is a risk of residual bias and confounding. In order to achieve a high level of accuracy in all collected data, especially the survival endpoints, multiple sources were utilized. In addition to the database of the Dutch Association of Urology, data was supplemented from the local patient charts, the National Cancer Registry (NCR) database, and municipal registers within the NCR database. The inclusion of these various sources facilitated thorough data collection and ensured sufficient follow-up time, resulting in complete and accurate information regarding disease survival. Nevertheless, the scoring of complications is prone to bias and fully dependent on correct registration. Further, there was no retrieval of data pertaining to adjuvant therapy or exact tumour recurrence. Worthy of note, our study only focused on the development of complications that scored at least grade 3 according to the Clavien-Dindo classification. Following this, a paralytic ileus that is treated with total parenteral nutrition or a wound infection that is not surgically treated are not considered grade 3 and were therefore not an endpoint for the purpose of this study.

5. Conclusion

Complications following RC are common and impactful. For this reason, the identification of risk factors and development of strategies for prevention and management of major complications after RC can improve health-related quality of life and reduces the burden of morbidity and mortality. The present study reflects the incidence of major complications following RC in real world settings in The Netherlands. More than a quarter of the patients developed a major complication after RC. The risk of major complications according to Clavien-Dindo was higher in men, in patients with higher ASA and CCI, and in patients who underwent open RC, high blood loss and longer duration of surgery. Patients suffering from a major complication also had worse overall survival compared to those who had no major complication.

Conflicts of Interest Statement

The authors declare that there is no conflict of interest. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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