Relationship between operative duration and perioperative outcomes after radical cystectomy

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FARAJ KS, JUDGE N, BLODGETT G, TYSON II MD. Relationship between operative duration and perioperative outcomes after radical cystectomy. *Can J Urol* 2021;28(2):10603-10609.

Introduction: *Prolonged operative times have been associated with an increased risk in complications in other major abdominal surgeries. This study tests the hypothesis that longer operative times will be associated with an increased risk in perioperative complications after radical cystectomy (RC).*
Materials and methods: *Adult patients who underwent RC from January 1, 2012, through December 31, 2016, were identified from the National Surgical Quality Improvement Program (NSQIP) database. A natural log transformation was used to determine cutoff points for operative times at 33rd, 67th, and 90th percentiles: 272, 371, and 479 minutes, respectively. Cohorts were A (≤ 272 min), B (273-371 min), C (372-479 min), and D (> 479 min). Multivariable logistic regression analysis was performed to identify associations between operative time and perioperative complications.*
Results: *Among 5,610 patients, the distribution across cohorts was A, 1,993 patients; B, 1,818; C, 1,171; and D, 628. Cohort D had a higher incidence of pulmonary embolism (PE), deep vein thrombosis (DVT), urinary tract infection (UTI), sepsis, 30-day readmission, and blood transfusion rate and had a longer median hospital length of stay. Multivariable analysis showed that operative time (per 60 min) was associated with increased risk of DVT (OR 1.10, p = .04), PE (OR 1.15, p = .01), UTI (OR 1.08, p = .004), readmission (OR 1.04, p = .03), and blood transfusion (OR 1.23, p < .001).*
Conclusions: *Longer operative times during RC are associated with a higher rate of perioperative complications. These findings may be confounded by disease stage, surgeon experience, variations in perioperative management protocols, or a combination of the above.*

Key Words: bladder cancer, urinary diversion, cystectomy, deep vein thrombosis, National Surgical Quality Improvement Program (NSQIP)

Accepted for publication February 2021

Acknowledgement
This study was generously supported by funding from the Robert D. and Patricia E. Kern Center for Health Care Delivery Science (M.D.T.), the Christian Haub Family Career Development Award for Cancer Research Honoring Dr. Richard Emslander (M.D.T.), and the Eric and Gail Blodgett Foundation (M.D.T.).

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Introduction

Overall complication rates after radical cystectomy (RC) are high, reported at about 60% in large series.[1,2] Operative duration can be long, with median times ranging from 330 to 464 minutes in some trials.[1,2] Longer operative times have been associated with increased complications in other major abdominal operations.[3,4] Certain factors can be associated with increased operative times, including case complexity, surgeon experience, minimally invasive approaches, and resident involvement.[5-7] Although patients undergoing RC have high complication rates in general, those who undergo prolonged operations may be at even higher risk for complications.

Prolonged operative times are not uncommon with RC in the modern era because increasingly, patients are undergoing a minimally invasive approach. The minimally invasive cystectomy, or robotic-assisted RC tends to take longer and can involve patients being in the lithotomy position for extended periods. Potential consequences include increased risk of compartment syndrome, thromboembolic events, and respiratory complications, which have been shown in other minimally invasive operations.[8] For example, longer operative times after radical prostatectomy have been associated with an increased rate of overall complications, including respiratory, genitourinary, and wound complications; readmission rate; and hospital length of stay (LOS).[9] The association between prolonged operative times and perioperative outcomes after RC has not been fully characterized.

In this context, we reviewed the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database to evaluate perioperative outcomes of patients undergoing RC, as a function of operative time. We hypothesized that longer operative times were associated with a greater incidence of postoperative complications. Implications of this study include provision of data to surgeons that could potentially assist in the modification of treatment approaches to reduce operative times and thus potentially reduce complication rates.

Materials and methods

Data source

This was a retrospective review of the NSQIP database. NSQIP is a prospective, multi-institutional database maintained by trained surgical clinical abstractors randomly assigned to review patients. It maintains the quality of its data through audits of randomized charts to identify reporting errors, which continue to be around 2%.[10]

Study population

The patient population of interest was selected with use of the Current Procedural Terminology codes 51570, 51575, 51580, 51585, 51590, 51595, and 51596. We excluded patients younger than 18 years, patients with benign disease, those with metastatic disease, and patients who underwent a simultaneous major abdominal operation not typically performed with cystectomy.

Measured variables

Data were collected on patient demographic characteristics, body mass index (BMI), smoking history, American Society of Anesthesiologists classification, and comorbidities. Procedural information included procedure date, surgical approach, operative time, and urinary diversion type. Postoperative variables included complications, hospital LOS, and hospital readmission.

Statistical methods

Statistical analyses were conducted with R version 3.4.4 software (R Project for Statistical Computing). Patient characteristics were summarized with mean (SD), median (interquartile range [IQR]), or number (percentage). A transformed operation time was used to determine the most relevant cutoff points for the cohorts. We considered a natural log transformation and a square root transformation. The square root transformation seemed the better fit for a normal distribution compared with the untransformed data and the log transformed data. We then identified the 33rd, 67th, and 90th percentiles of the transformed data and squared those numbers to find the corresponding operation time. The resulting cohorts were A (≤ 272 min), B (273-371 min), C (372-479 min), and D (> 479 min).

All p values were 2-sided, and $p < .05$ was considered statistically significant. A Kruskal-Wallis test was used to compare continuous variables; categorical variables were evaluated with Pearson χ^2 test or Fisher exact test. Multivariable regression models were constructed to test for associations between covariates and the outcomes of interest. Operative time was treated as a continuous variable with time measured in 60-minute intervals. Confounders included in the regression models were age, BMI, surgical approach, history of smoking, history of diabetes mellitus, urinary diversion type, and performance status. Since the missing values were minimal, we performed a complete case analysis.

Results

Four cohorts were obtained from a total of 5,610 patients, Table 1. Patients were youngest and the operations more common in the later years of the analysis for cohort A. This cohort consisted of patients with the lowest median BMI ($p < .001$), the lowest frequency of patients who underwent robotic RC (3.9%, $p < .001$) and the lowest frequency of patients who underwent a neobladder diversion (10.8%, $p < 0.001$). No other factors were statistically different between the groups at baseline. The median (IQR) operative time in patients who underwent an open RC versus robotic RC was 303.00

TABLE 1. **Baseline patient characteristics**[a]

Characteristic	A (n = 1,993)	B (n = 1,818)	C (n = 1,171)	D (n = 628)	Total (n = 5,610)	p value
Operative time, min	< 272	273-371	372-479	> 479		
Age, median (IQR), y	72 (65-79)	69 (62-76)	68 (61-75)	65 (56-74)	69 (62-76)	< .001
Female sex	322 (16.2)	327 (18.0)	219 (18.7)	125 (19.9)	993 (17.7)	.10
Year of operation					.002	
2012	224 (11.2)	204 (11.2)	113 (9.6)	66 (10.5)	607 (10.8)	
2013	290 (14.6)	321 (17.7)	228 (19.5)	105 (16.7)	944 (16.8)	
2014	371 (18.6)	380 (20.9)	253 (21.6)	152 (24.2)	1,156 (20.6)	
2015	481 (24.1)	394 (21.7)	257 (21.9)	135 (21.5)	1,267 (22.6)	
2016	627 (31.5)	519 (28.6)	320 (27.3)	170 (27.1)	1,636 (29.2)	
Diabetes mellitus					.70	
Yes, insulin therapy	128 (6.4)	123 (6.8)	84 (7.2)	44 (7.0)	379 (6.8)	
No	1,617 (81.1)	1,455 (80.0)	918 (78.4)	508 (80.9)	4,498 (80.2)	
Yes, no therapy	248 (12.4)	240 (13.2)	169 (14.4)	76 (12.1)	733 (13.1)	
History of smoking	467 (23.4)	435 (23.9)	279 (23.8)	166 (26.4)	1,347 (24.0)	.49
History of COPD	164 (8.2)	142 (7.8)	79 (6.7)	44 (7.0)	429 (7.6)	.44
History of CHF	10 (0.5)	11 (0.6)	10 (0.9)	4 (0.6)	35 (0.6)	.68
Neobladder	215 (10.8)	257 (14.1)	244 (20.8)	200 (31.9)	916 (16.3)	< 0.001
Performance status					.45	
Independent	1,930 (96.8)	1,767 (97.2)	1,151 (98.3)	616 (98.1)	5,464 (97.4)	
Partially dependent	40 (2.0)	35 (1.9)	12 (1.0)	7 (1.1)	94 (1.7)	
Totally dependent	19 (1.0)	14 (0.8)	6 (0.5)	4 (0.6)	43 (0.8)	
Unknown	4 (0.2)	2 (0.1)	2 (0.2)	1 (0.2)	9 (0.2)	
Robotic approach	73 (3.7)	227 (12.5)	205 (17.5)	130 (20.7)	635 (11.3)	< .001
BMI, median (IQR), kg/m^2	26.9 (24.1-30.2)	28.0 (24.8-31.6)	28.3 (25.4-32.2)	29.1 (25.7-33.6)	27.8 (24.7-31.5)	< .001

BMI = body mass index; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; IQR = interquartile range
[a]values are presented as number (percentage) of patients unless specified otherwise

(235.0-390.0) versus 379.0 (319.0-459.0) minutes, respectively ($p < 0.001$) and the median (IQR) operative time in patients who underwent a neobladder diversion versus ileal conduit was 364 .0 (280.0-461.8) versus 305.0 (236.0-389.0) minutes, respectively ($p < 0.001$).

In the evaluation of perioperative outcomes, Table 2, patients in cohort D had a greater incidence of deep vein thrombosis (DVT) and thrombophlebitis events ($p = .03$), pulmonary embolism (PE) ($p = .04$), urinary tract infection (UTI) ($p < .001$), hospital readmissions ($p < .001$), and perioperative blood transfusions ($p < .001$). In addition, cohort D had the longest hospital LOS ($p < .001$).

A multivariable regression analysis was performed to further characterize the relationship between operative time and the outcomes of interest, Table 3. The outcomes for this analysis were DVT, PE, blood transfusion, hospital LOS, UTI, hospital readmission, superficial surgical infection (SSI), and deep surgical infection (DSI).

On multivariable regression analysis, increased operative time was associated with the following

TABLE 2. **Outcomes of the cohorts**[a]

Outcome	A (n = 1,993)	B (n = 1,818)	C (n = 1,171)	D (n = 628)	Total (n = 5,610)	p value
Operative time, min	< 272	273-371	372-479	> 479		
Pneumonia	62 (3.1)	58 (3.2)	27 (2.3)	9 (1.4)	156 (2.8)	.07
Pulmonary embolism	24 (1.2)	27 (1.5)	21 (1.8)	20 (3.2)	92 (1.6)	.004
Deep vein thrombosis	40 (2.0)	41 (2.3)	23 (2.0)	25 (4.0)	129 (2.3)	.03
Cardiac arrest	18 (0.9)	15 (0.8)	10 (0.9)	7 (1.1)	0 (0.9)	.83
Myocardial infarction	32 (1.6)	27 (1.5)	19 (1.6)	8 (1.3)	86 (1.5)	.85
Urinary tract infection	126 (6.3)	160 (8.8)	114 (9.7)	74 (11.8)	474 (8.4)	< .001
Cerebrovascular accident	8 (0.4)	10 (0.6)	3 (0.3)	0 (0)	21 (0.4)	.26
Blood transfusion	614 (30.8)	625 (34.4)	452 (38.6)	307 (48.9)	1,998 (35.6)	< .001
Superficial site infection	105 (5.3)	108 (5.9)	69 (5.9)	49 (7.8)	331 (5.9)	.14
Deep site infection	24 (1.2)	27 (1.5)	16 (1.4)	10 (1.6)	77 (1.4)	.85
Renal insufficiency	43 (2.2)	24 (1.3)	21 (1.8)	15 (2.4)	103 (1.8)	.18
Length of stay, d						< .001
Mean (SD)	9.84 (7.8)	9.04 (6.7)	9.57 (7.8)	10.39 (7.4)	9.59 (7.4)	
Median (IQR)	7 (3-11)	7 (3-11)	7 (3-11)	8 (3-14)	7 (3-11)	
Readmission	323 (16.2)	370 (20.4)	263 (22.5)	164 (26.1)	1,120 (20.0)	< .001

[a]values are presented as number (percentage) of patients unless specified otherwise.

outcomes: DVT or thrombophlebitis events (OR 1.1; 95% CI, 1.0-1.2; p = .01), PE (OR 1.2; 95% CI, 1.1-1.3; p = .002), UTI (OR 1.09; 95% CI, 1.04-1.14; p < .001), hospital readmission (OR 1.1; 95% CI, 1.06-1.14; p < .001), and perioperative blood transfusion (OR 1.22; 95% CI, 1.18-1.25; p < .001). Operative time was no longer associated with hospital LOS.

Discussion

In the present retrospective review of 5,610 adults undergoing RC with urinary diversion, we identified a relationship between prolonged operative times and adverse perioperative outcomes. Specifically, patients were at increased risk for DVT, PE, perioperative blood transfusion, and UTI. Prolonged operative time was also associated with an increased risk of 30-day hospital readmission.

Prolonged operative times have been associated with an increased risk of complications in other major abdominal operations. For instance, in a systematic review of 66 studies that evaluated various surgical specialties, Cheng et al[3] identified a 14% increase in the likelihood of complications per unit time when all specialties were evaluated. In seven urologic studies, the pooled OR for risk of complication per unit time was 1.02. Ng et al[11] evaluated the perioperative outcomes among 187 patients undergoing robot-assisted versus open RC and investigated the factors associated with a perioperative complication after surgery. On multivariable analysis, prolonged operative time was identified as a predictor of major complications at 30 days. However, the study did not elaborate on the effect of operative time on specific complications

We present a more comprehensive analysis that quantified the effect of operative time on various complications, many of which were consistent with prior studies that evaluated this relationship in other surgical procedures. In regards to thromboembolic events, Kim et al[4] examined the association of surgical duration and incidence of venous thromboembolism (VTE) among 1,432,855 patients undergoing surgery with general anesthesia in 315 hospitals participating in NSQIP from 2005 through 2011. Their study found that prolonged operative times carried a 1.27-fold increase in odds of developing a VTE. The study evaluated the three most common procedures—laparoscopic cholecystectomy, appendectomy, and gastric bypass—and reported an 18% to 26% increase in risk of VTE per unit time increase.[4] This risk is thought to be due to an increase in blood stasis, endothelial damage, and a hypercoagulable state in prolonged

	DVT		PE		UTI		DSI		SSI		Readmission		Any		LOS	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	Estimate (95% CI)	p value
Intercept	0.0 (0.0-0.0)	< .001	0.0 (0.0-0.0)	< .001	0.04 (0.01-0.1)	< .001	0.0 (0.0-0.0)	< .001	0.01 (0.00-0.02)	< .001	0.04 (0.02-0.08)	< .001	0.11 (0.06-0.2)	< .001	3.7 (1.8-5.6)	< .001
Operation time (h)	1.1 (1.0-1.2)	.04	1.2 (1.0-1.3)	.01	1.1 (1.0-1.1)	.004	1.1 (0.9-1.2)	.38	1.0 (1.0-1.1)	.26	1.04 (1.0-1.1)	.03	1.20 (1.1-1.2)	< .001	0.0 (−0.1 to 0.1)	.93
Robotic procedure	0.9 (0.5-1.6)	.75	1.2 (0.6-2.1)	.63	1.4 (1.1-1.3)	.01	0.10 (0.01-0.8)	.03	0.4 (0.2-0.7)	< .001	1.4 (1.1-1.7)	.004	0.5 (0.4-0.5)	< .001	−1.03 (−1.6 to −0.4)	< .001
Smoking	1.1 (0.7-1.7)	.64	0.7 (0.4-1.1)	.15	1.1 (0.8-1.3)	.59	1.2 (0.7-2.2)	.46	1.2 (0.9-1.5)	.31	1.1 (0.9-1.2)	.58	1.0 (0.8-1.1)	.58	0.6 (0.2-1.1)	.007
Age	1.02 (1.0-1.04)	.06	1.00 (1.0-1.1)	.74	0.99 (0.98-1.0)	.13	1.01 (0.99-1.04)	.29	1.00 (0.99-1.01)	.85	1.00 (0.99-1.01)	.73	1.02 (1.01-1.02)	< .001	0.06 (0.04-0.08)	< .001
Diabetes mellitus	0.5 (0.3-0.9)	.02	0.8 (0.4-1.3)	.31	1.0 (0.7-1.2)	.69	1.3 (0.8-2.2)	.29	1.2 (0.9-1.4)	.16	1.3 (1.1-1.5)	.004	1.3 (1.2-1.5)	< .001	0.01 (−0.5 to 0.5)	.97
Neobladder	1.4 (0.0-2.2)	.15	1.1 (0.6-1.9)	.63	1.5 (1.2-2.0)	< .001	1.4 (0.8-2.5)	.26	1.0 (0.7-1.4)	.94	1.4 (1.1-1.6)	< .001	1.1 (0.9-1.3)	.23	0.02 (−0.5 to 0.5)	.94
ECOG: partially dependent vs. independent	1.1 (0.2-3.6)	.90	1.5 (0.2-5.0)	.57	0.5 (0.2-1.3)	.21	1.8 (0.4-7.5)	.44	2.0 (0.9-3.8)	.0496	0.5 (0.3-1.0)	.06	1.5 (1.0-2.3)	.06	2.9 (1.4-4.3)	< .001
ECOG: totally dependent v.s independent	3.17 (0.5-11.3)	.13	1.74 (0.1-9.0)	.60	3.62 (1.6-7.5)	<.001	0.0 (0.0-0.0)	>.99	2.21 (0.7-5.5)	.12	1.24 (0.6-2.5)	.57	2.57 (1.4-5.1)	.005	6.01 (3.9-8.2)	< .001
BMI	1.03 (1.0-1.1)	.05	1.04 (1.0-1.1)	.02	1.03 (1.01-1.1)	< .001	1.08 (1.05-1.11)	< .001	1.08 (1.06-1.09)	< .001	1.03 (1.02-1.04)	< .001	1.01 (1.00-1.02)	.15	0.00 (-0.03-0.03)	.97
Blood transfusion	1.6	.009	1.0 (0.6-1.6)	.96	1.0 (0.8-1.2)	.76	1.4 (0.9-2.2)	.19	1.2 (0.9 to 0.2)	.17						
Total No. of complications											1.4 (1.4-1.5)	< .001			1.5 (1.4 to 1.7)	< .001

BMI = body mass index; DSI = deep site infection; DVT = deep vein thrombosis; ECOG = Eastern Cooperative Oncology Group; LOS = length of stay; OR = odds ratio; PE = pulmonary embolism; SSI = superficial site infection; UTI = urinary tract infection

TABLE 1. **Multivariable regression model for complications evaluated by time per hour**

operations. Another study by Lyon et al looked specifically at trends of VTE after RC over time between 2011 and 2016 using the NSQIP database. Operative time was divided into quartiles and the authors found that longer operative times were associated with increased risk of VTE (OR, 1.71; p < .05).[12]

In our study, besides similarly stratifying cohorts into categorical groups and observing a trend of increased VTE in the cohorts with the longer operative times, we quantified the effect of operative time on the risk of developing a DVT or PE. For instance, we observed a 12% and a 17% increase in risk of DVT and PE per additional 60 minutes of operative time, respectively. Although this association is similar to prior reports, other factors could not be accounted for in the models we used that would likely affect the outcome, including cancer stage, perioperative VTE prophylactic therapy, and extended VTE prophylactic therapy. An especially important factor to consider in the modern era is extended VTE prophylactic therapy, which has been shown to reduce VTE incidence among patients undergoing major surgery, including RC. For instance, use of extended VTE prophylaxis reduced the risk of VTE in patients undergoing major pelvic cancer surgery in a trial that evaluated nonurologic malignancies.[13] Additionally, an investigation of the role of extended-duration venous thromboprophylaxis after RC yielded encouraging results. Pariser et al[14] also assessed 402 patients who underwent RC before and after implementation of an extended thromboprophylaxis regimen of 28 days of enoxaparin at a single institution. They reported a significantly lower rate of VTE in the extended prophylaxis cohort (12% versus 5%, p = .02) and the extended regimen was significantly associated with reduced odds of VTE (OR 0.33) on multivariable analysis.

The present study also found that UTI was associated with prolonged operative times. In prior studies, this outcome has been associated with longer operations, and investigators have suggested that the pathophysiologic factors may be related to prolonged catheterization during the long operations.[15,16] However, this clinical outcome may not be as relevant for RC since cases of RC are contaminated, where urine is in contact with bowel and fecal contents because of the urinary diversion. Although catheters are placed during the procedure and stay in place for several hours, other confounding factors likely contribute to this risk, including aspects of the urinary diversion (ie, fecal contamination), BMI, and patient comorbidities. For instance, cohort D, the group with the highest incidence of UTI, included patients with the highest BMI and patients who underwent a robotic approach. Interestingly, BMI has reportedly been associated with increased development of UTIs after a major abdominal surgery, including RC.[17] In addition, some investigators have suggested that robotic RC may be associated with an increased incidence of UTI, although this was not a statistically significant finding.[18] Because we observed an association of both elevated BMI and robotic RC with UTI, we accounted for these factors in the multivariable regression analysis. However, operative time was still associated with an increased UTI risk. It is possible that additional unmeasured confounding factors relate to the increased operative time that places these patients at risk for UTI (ie, fecal contamination, prolonged ureteral clamping times, the time needed for urinary diversion, stent duration, and perioperative and post hospital discharge antibiotic status). However, this outcome is less clear at this time.

The risk of blood transfusion has also been reported as a factor associated with prolonged operations in other abdominal surgeries.[19] Similarly, we found this was the case in RC. But again, this outcome may be confounded by critical components not reported in NSQIP, such as surgical difficulty, tumor stage or grade, and surgeon experience.[6] Other outcomes that had an association with longer operative times in our study include hospital readmission and hospital LOS. Because longer operative times can be associated with greater morbidity after surgery, it is not surprising to also observe more frequent hospital readmissions and longer hospital LOS in cases with prolonged operative times. Although we attempted to correct for complications in the regression model, Table 3, the operative time continued to be associated with hospital readmission. Unreported components such as patient, physician and institutional factors may be contributing to this association.

Surgical approach has been investigated as a potential component that can contribute to prolonged operative times and complications at the time of RC. Notably, in the Memorial trial, Bochner et al assessed 90 day complications after RC and with the exception of a lower mean intraoperative blood loss and lower incidence of wound complications in the robotic cohort, found similar complication rates between robotic and open approaches.[2] The choice of urinary diversion has also been a relevant factor that can affect operative time, but no definitive conclusions have been confirmed regarding complications rates between neobladder and ileal conduit diversion, though a higher incidence of UTI and hospital readmission has been reported in patients who undergo a neobladder diversion.[20-22] In our study, the median operative time was significantly greater in patients who underwent a robotic RC and these patients had a slightly higher risk of developing a UTI and experiencing a hospital readmission. However, the robotic approach was associated with a lower risk of developing a superficial or deep wound infection and any complication. In addition, patients who underwent a robotic RC experienced an approximately 1 day shorter hospital LOS. On a similar note, a neobladder diversion was also associated with a longer operative duration, greater risk of developing a UTI, and hospital readmission. However, as discussed in prior sections, it is not clear whether complications associated with surgical approach and/or diversion type are a function of the approach/diversion type itself or due to confounding, unreported factors that may be present at the time of surgery.

Limitations

The present study has limitations. Although NSQIP is a prospectively maintained database, the data review was retrospective in nature. The most important finding that we report is the increased risk of VTE associated with operative time. We attempted to correct for covariates in both regression models, but we were not able to evaluate several important factors (ie, cancer stage, coagulopathies, and thromboprophylaxis status). Additionally, the cancer stage was not available, and this detail may be important because disease stage could be associated with several outcomes, including VTE, transfusion rate, and surgical difficulty. Surgeon experience may also be an important factor that can affect operative duration and complications, but this variable was not available. Additionally, operative information was not available, such as the time for the urinary diversion, stent duration, and perioperative and postdischarge medication status, which could potentially affect the risk of developing a complication.

Despite these limitations, the present study provides a comprehensive assessment on the effect of operating time on the development of complications after RC.

We believe that the information provides useful details to surgeons to prepare or treat patients who are likely to undergo a prolonged operation. Such at-risk patients may include those with advanced disease, undergoing concomitant procedures (eg, nephrectomy) with inexperienced surgeons. When provided with such information, urologists may elect to modify management options in the perioperative setting (eg, provide extended thromboprophylaxis, referral to a tertiary care center).

Conclusions

In conclusion, RC with urinary diversion is a major procedure that is associated with high complication rates. The operative time is long and can be associated with increased risk of perioperative complications such as VTE, perioperative blood transfusion, UTI, and hospital readmission. □

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