Original article

Comprehensive characterization of perioperative reoperation following radical cystectomy

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Abstract

Introduction: To examine the nature, timing, and risk factors underlying return to the operating room (ROR) following radical cystectomy (RC). ROR has been proposed as a surgical quality metric based on data from the general surgery literature, but ROR has not been comprehensively characterized following RC.

Patients and methods: We queried our institutional Cystectomy Registry from 2000 to 2016 to identify patients with ROR within 90 days of RC. Multivariable logistic regression was used to examine associations between patient features and ROR. Survival outcomes were studied based on whether ROR was necessary.

Results: Of 1968 patients treated with RC, 112 (5.7%) underwent 125 reoperations within 90 days of RC, of which 93% were unanticipated and due to postsurgical complications. The most common reasons for ROR were facial dehiscence (29%), bowel obstruction (21%), and enteric anastomotic leak (8%). On multivariable analysis, increasing body mass index (odds ratio 1.04, 95% confidence interval (CI) 1.01−1.08, $P = 0.045$) and albumin <3.5 g/dl (odds ratio 2.15, 95% CI 1.28−3.59, $P = 0.004$) were associated with greater odds of ROR. Patients with a ROR had significantly decreased 5-year overall survival compared to patients who did not undergo ROR (43% vs. 55%; $P = 0.003$), and ROR was associated with increased all-cause mortality after multivariable adjustment (hazard ratio 1.33, 95% CI 1.01−1.74, $P = 0.04$).

Conclusion: ROR principally occurred due to unanticipated complications and was associated with increased mortality after RC. These data suggest ROR may be a useful metric by which urological programs can track the efficacy of interventions aimed at improving perioperative care for RC patients. © 2018 Elsevier Inc. All rights reserved.

Keywords: Postoperative complications; Bladder cancer; Radical cystectomy; Reoperation

1. Introduction

Unplanned return to the operating room (ROR) has been proposed as a quality indicator following major surgery [1,2]. Unplanned ROR within 30 days of an index operation is reported by the American College of Surgeons national surgical quality improvement program database [3,4], and reintervention rates have been tracked following centralization of RC in England [5]. ROR has been associated with an increased risk of mortality as well as increased resource utilization following general and vascular surgical procedures [1,2,6]. However, the nature, timing, and risk factors underlying ROR after radical cystectomy (RC) have not been completely characterized.

Developing a clear understanding of ROR as it relates to RC is essential for informing its usefulness as a metric of surgical quality in urology. The overall rate of reoperations after RC has been well described, and has been observed to occur in 3−7% of cases [7−9]; however, the proportion of RORs that are unanticipated at the time of RC, as well as the proportion that are attributable to postsurgical complications, is less well understood. Further, data in

nonurologic surgery has suggested an association between ROR and inferior overall survival, but it is not known whether this association holds true for patients undergoing RC [1,2,6].

To address this knowledge gap, the purpose of the present study was to comprehensively characterize the etiology of and risk factors for ROR following RC at a single tertiary referral center, and to investigate an association between ROR and survival outcomes.

2. Methods

2.1. Study population

Following institutional review board approval, we queried the prospectively populated Mayo Clinic Cystectomy Registry for patients who underwent RC between 2000 and 2016. Patient features assessed included age, gender, race, Eastern Cooperative Oncology Group status, body mass index (BMI), history of coronary artery disease or myocardial infarction, peripheral vascular disease (inclusive of claudication, cerebrovascular accident, or transient ischemic attack), hypertension, chronic obstructive pulmonary disease, diabetes, preoperative renal insufficiency (creatinine > 2 mg/dl), preoperative serum albumin, smoking status, prior kidney transplant, and receipt of neoadjuvant or adjuvant chemotherapy. Comorbid conditions were assessed individually rather than as a comorbidity index given prior evidence of association of conditions such as chronic obstructive pulmonary disease with postoperative complications requiring ROR [10,11]. Operative variables included attending surgeon, total number of lymph nodes dissected, positive surgical margin, operative time, estimated blood loss, perioperative transfusion, and surgical approach. Urinary diversion was characterized as continent (continent cutaneous or orthotopic neobladder) or incontinent (ileal conduit, colon conduit, or cutaneous ureterostomy). Pathologic stage is reported as per the American Joint Committee on Cancer TNM system, 7th edition [12].

2.2. Outcomes

The primary outcome was ROR, defined as any return to a surgical operating room within 90 days of RC, which is a prospectively tracked endpoint. Reoperations that occur outside of our institution are captured through correspondence with patients and outside providers or during subsequent patient encounters with our department. Gastrointestinal

endoscopy and interventional radiology procedures were not considered ROR. Reasons for ROR were determined via re-review of patient records by a single investigator blinded to patient survival (TDL). Unplanned ROR was classified according to the American College of Surgeons definition as any ROR that was not planned prior to exit from the operating room during the index procedure [3]. Unplanned ROR was then further subdivided as related to complications from RC (e.g. fascial dehiscence) or unrelated to RC (e.g. biliary colic from cholelithiasis requiring interval cholecystectomy) as per a recently published definition [4].

Secondary outcomes included cancer specific and overall survival. Survival data are assessed in the cystectomy registry annually, and causes of death are determined from death certificates or physician correspondence.

2.3. Statistical analysis

Patient features are summarized with frequencies and percentages as well as medians with interquartile range. Continuous features were compared using the Mann-Whitney U test, and categorical features using chi-square or Fisher's exact tests. A multivariable logistic regression model examining predictors of ROR was fit using all pre- and intraoperative variables with $P \leq 0.1$ on univariable analysis as well as the a priori predictors age, Eastern Cooperative Oncology Group status, pathologic T stage, and surgical approach. Perioperative blood transfusion was significantly associated with ROR on univariable analysis, but not included in the multivariable model because this variable includes transfusions given after the index operation during the perioperative hospital stay; because this could include transfusions given during the reoperation itself, it was not assessed as a risk factor for ROR. Survival was estimated using the Kaplan-Meier method and compared with the log-rank test. Cox proportional hazards models were used to assess predictors of survival. Preoperative serum albumin was missing in 457 patients (23%). These missing values were imputed using an iterative nonparametric technique based on a random forest [13] and all multivariable models were performed twice—once including observed and imputed albumin levels, and once after removing albumin as a covariate. A $P < 0.05$ was considered significant. All analyses were 2-tailed and performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.2.3 (R Foundation for Statistical Computing; Vienna, Austria).

3. Results

A total of 1,968 patients were identified. Baseline characteristics of the study cohort are found in Table 1. Median follow up among those alive at last contact was 5.4 years (IQR 2.2−9.6 years), during which time 1,047 patients died, 687 from bladder cancer. We identified 112 (5.7%) patients who underwent 125 reoperations within 90 days of RC. The ROR was within 30 days of RC for 93 (83%) patients and between 31 and 90 days for 19 (17%) patients. Seventy-eight (4.0%) patients died within 90 days of RC;

of these, 16 (21%) experienced an ROR prior to death. There was no significant difference in ROR rate based on surgical approach (2.6% robotic vs. 5.9% open, $P = 0.09$) or among those treated with neoadjuvant chemotherapy (7.6% with vs. 5.3% without, $P = 0.09$). The association between attending surgeon and ROR was not statistically significant ($P = 0.29$, Supplementary Table 1).

The etiologies for ROR are summarized in Table 2. Of the 112 primary RORs, 104 (93%) were unplanned due to complications from RC, 7 (6%) were unplanned but unrelated to RC, and 1 (0.9%) was planned. The most common reasons for unplanned related ROR were facial dehiscence (33/112, 29%), bowel obstruction (23/112, 21%), and enteric anastomotic leak (9/112, 8%). Reasons for unplanned unrelated ROR included malignant bowel obstruction due to peritoneal carcinomatosis not present at time of RC (2/112, 1.8%), and a single episode each of urethrectomy for positive urethral margin, incarcerated inguinal hernia, biliary colic from cholelithiasis, percutaneous nephrolithotomy for stone not recognized preoperatively, and excisional cervical lymph node biopsy (1/112, 0.9% for each). The single planned reoperation was creation of an arteriovenous fistula in the setting of preoperative renal insufficiency for which a temporary dialysis catheter was placed at RC. Eight patients had 2 or more ROR, as described in Supplementary Table 2.

On multivariable logistic regression (Table 3), patient features associated with significantly increased odds of ROR included increasing BMI (odds ratio 1.04, 95% confidence interval [CI] 1.01−1.08, $P = 0.045$) and albumin <3.5 g/dl (odds ratio 2.15, 95% CI 1.28−3.59, $P = 0.004$). On sensitivity analysis excluding albumin as a covariate, significance of the results did not change, as BMI ($P = 0.04$) remained the only factor significantly associated with ROR (Supplementary Table 3).

Moreover, we found that patients who experienced a ROR had significantly decreased 5-year cancer specific (53% vs. 64%, $P = 0.03$) and OS (43% vs. 55%; $P = 0.003$) compared to those without ROR (Fig. 1). After adjustment for clinical and pathologic features, ROR remained associated with greater risk of all-cause mortality (hazard ratio 1.33, 95% CI 1.01−1.74; $P = 0.04$) but not cancer-specific mortality ($P = 0.07$) (Table 4). In a sensitivity analysis excluding albumin as a covariate, both the point estimate for the hazard ratio and the significance of ROR in terms of its association with all-cause mortality were unchanged (Supplementary Table 4).

4. Discussion

In a single institution series of 1968 RC patients, we observed that ROR occurred primarily as a result of unanticipated complications and was associated with increased all-cause mortality. The observed ROR rate of 5.7% was within the expected range of 3 to 7% from previously published series [7−9]. Almost all RORs were related to postsurgical complications (93%), with the most common reasons being facial dehiscence and bowel obstruction. Patients experiencing an ROR had inferior survival outcomes, consistent with what has been demonstrated in the general surgery literature [1,2,6]. Taken together, these data suggest the opportunity for RLOR to be of utility for monitoring efforts aimed at effecting process improvement for RC patients.

The optimal use of ROR as a metric of surgical quality deserves careful consideration. Some indications for ROR are subjective, such as when to operate on a patient with a bowel obstruction. Bowel obstruction was responsible for 21% of the RORs in this series, and rates may be influenced by local practice patterns. We therefore agree with the suggestion by Birkmeyer [1] that ROR may be most useful as a metric of surgical quality at a local level, and could be used within institutions for measuring efficacy of techniques aimed at decreasing reoperative complications, including robotic or enhanced recovery after surgery programs. However, ROR may also be of use on a systems level to assess the impact of centralization of RC to specialized centers. The British experience has shown that rates of reintervention following RC significantly decreased in parallel with centralization of care, however given the reported rates (30%) this definition likely includes interventional procedures in addition to reoperations [5]. ROR could therefore be utilized to assess the impact of RC centralization in other countries or healthcare systems. Further, the degree to which the identified risk factors for ROR are modifiable remains an area of active research. Given this uncertainty, our data suggest that ROR rates after RC might be optimally reported along with BMI and albumin levels to inform the underlying level of risk in the assessed populations.

We and others have observed an association between obesity and ROR [6,11]. Obesity has previously been linked to an increased risk of wound complications after RC, which accounted for 32% of re-operative interventions in the present series [14,15]. Perioperative use of broad-spectrum antibiotic and antifungal agents have been shown to reduce the odds of wound infection after RC [15]; this may be an effective strategy for reducing ROR rate in obese patients, although this requires further study. Existing data are conflicting regarding prophylactic subcutaneous drain placement in obese patients to decrease the rate of surgical site infection, but this may likewise be an area suitable for future inquiry [16,17].

Preoperative hypoalbuminemia has been associated with an increased risk of morbidity and mortality following RC [18−20], and has also been found to increase risk of anastomotic leakage after colorectal resection [21]. Consistent with these data, a serum albumin <3.5 g/dl was associated with twice the odds of a re-operative complication in this series. Hypoalbuminemia is associated with both nutritional deficiency and systemic inflammation [19,20]. Studies in hypoalbuminemic mice reveal a depleted immune response

Table 1
Characteristics of the study cohort

	No ROR, $n = 1856$	ROR, $n = 112$	*P* value
Age, y, median (IQR)	68 (61−75)	69 (63−77)	0.14
Race			0.76
Caucasian	1,726 (93%)	105 (94%)	
Non-Caucasian	130 (7%)	7 (6%)	
Male sex	1,529 (82%)	99 (88%)	0.10
Year of surgery			0.28
2000−2008	1,028 (55%)	57 (51%)	
2009−2017	828 (45%)	55 (49%)	
ECOG ($n = 1,904$)			0.20
0	1,520 (85%)	84 (79%)	
1	203 (11%)	18 (17%)	
$\geq$2	74 (4%)	5 (4.7%)	
BMI, kg/m^2, median (IQR) ($n = 1,896$)	27.9 (25−31)	28.8 (26−33)	0.02
CAD/MI ($n = 1,871$)	451 (26%)	28 (26%)	0.84
PVD ($n = 1,867$)	229 (13%)	17 (16%)	0.35
Hypertension ($n = 1,904$)	926 (52%)	67 (63%)	0.03
COPD	117 (6%)	35 (31%)	<0.001
Diabetes ($n = 1,868$)	302 (17%)	19 (18%)	0.84
Preoperative renal insufficiency ($n = 1,902$)	102 (6%)	7 (7%)	0.88
Preoperative albumin, g/dl			<0.001
Missing	434 (23%)	23 (21%)	
$\geq$3.5	1,250 (67%)	65 (58%)	
<3.5	172 (9%)	24 (21%)	
Current/former smoker ($n = 1,901$)	1,381 (74%)	83 (74%)	0.67
Prior kidney transplant	4 (0.2%)	0 (0%)	0.77
Neoadjuvant chemotherapy ($n = 1,960$)	315 (17%)	26 (23%)	0.09
Adjuvant chemotherapy ($n = 1,927$)	244 (13%)	10 (9.0%)	0.18
Surgical approach			0.09
Open	1,708 (92%)	108 (96%)	
Robotic	148 (8%)	4 (4%)	
Continent diversion ($n = 1,958$)	541 (29%)	33 (30%)	0.97
Pathologic T stage ($n = 1,941$)			0.19
<T2	869 (47%)	47 (42%)	
T2	303 (16%)	20 (18%)	
T3	512 (28%)	26 (23%)	
T4	148 (8%)	16 (14%)	
Pathologic node positive ($n = 1,952$)	364 (20%)	27 (24%)	0.35
Pathologic CIS ($n = 1,935$)	796 (44%)	42 (39%)	0.30
Total lymph nodes removed, median (IQR) ($n = 1,946$)	18 (9−27)	20 (9−26)	0.70
Positive surgical margin	27 (2%)	2 (2%)	0.94
Operative time, min, median (IQR) ($n = 1,470$)	299 (249−353)	300 (269−359)	0.32
EBL, ml, median (IQR) ($n = 1,965$)	600 (400−950)	700 (450−1050)	0.01
Perioperative blood transfusion	913 (49%)	74 (66%)	0.001

BMI = body mass index; CAD/MI = coronary artery disease or history of myocardial infarction; COPD = chronic obstructive pulmonary disease; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; PVD = peripheral vascular disease (inclusive of claudication, cerebrovascular accident, or transient ischemic attack); ROR = return to the operating room; CIS = carcinoma in situ; TNM = tumor, node, metastasis staging; T.D.L. = Timothy D. Lyon (first author).

to stress [22], which may help explain why such patients have impaired wound healing and appear more susceptible to postoperative infection [18−21]. Emerging data suggests that perioperative immunonutrient supplementation may help decrease these risks, although an appropriately powered randomized trial has not yet been performed among RC patients [23−25].

Whether differences in surgical approach could impact the rate of ROR for fascial dehiscence, the most common reason for ROR in this series, remains unanswered from the present analysis. Hussein et al. recently reported the rate of ROR following robotic RC, and found that only 3% of their re-operative complications were due to fascial dehiscence−considerably lower than the 29% rate reported here, where the majority of procedures were performed in an open fashion [9]. It makes intuitive sense that fascial dehiscence might be less common in patients undergoing robotic RC given the smaller incision size; however, given the low number of robotic procedures requiring ROR presented here ($n = 4$) and inherent

Table 2
Reasons for primary return to the operating room

Reason	0−30 d, n = 93	31−90 d, n = 19	Overall, n (%)
Wound			
Fascial dehiscence	31	2	33 (29)
Would exploration/washout	3	−	3 (3)
Vaginal cuff dehiscence	1	1	2 (2)
Incisional hernia repair	−	1	1 (0.9)
Gastrointestinal			
Bowel obstruction	19	4	23 (21)
Enteric anastomotic leak	8	1	9 (8)
Unrecognized enterotomy/peritonitis	3	−	3 (3)
Cholecystectomy	2	−	2 (2)
Strangulated inguinal hernia	1	−	1 (0.9)
Perforated duodenal ulcer	1	−	1 (0.9)
Rectal stump leak	−	1	1 (0.9)
Genitourinary			
Neobladder rupture/leak	4	2	6 (5)
Ureteral stent for stricture	−	2	2 (2)
Conduit revision (necrosis)	1	1	2 (2)
Unrecognized ureteral duplication	1	−	1 (0.9)
Completion urethrectomy	1	−	1 (0.9)
Retained ureteral stent	1	−	1 (0.9)
Drainage scrotal fluid	−	1	1 (0.9)
Percutaneous nephrolithotomy	−	1	1 (0.9)
Cardiovascular			
Uncontrolled hemorrhage	5	−	5 (4)
Coronary artery bypass graft	2	−	2 (2)
Intra-aortic balloon pump (myocardial infarction with hemodynamic instability)	1	−	1 (0.9)
Transvenous pacemaker (refractory atrial fibrillation)	1	−	1 (0.9)
Below knee amputation for acute limb ischemia	1	−	1 (0.9)
Pulmonary embolectomy	1	−	1 (0.9)
Acute mesenteric ischemia	1	−	1 (0.9)
Axillary-femoral bypass	1	−	1 (0.9)
Arteriovenous fistula	1	−	1 (0.9)
Other			
Retained Jackson-Pratt drain	1	−	1 (0.9)
Cervical lymph node biopsy	1	−	1 (0.9)
Laparoscopic lymphocele unroofing	−	1	1 (0.9)
Transperineal abscess drainage	−	1	1 (0.9)

Table 3
Multivariable logistic regression of factors predicting return to operating room

Feature	Adjusted odds ratio (95% CI)	P Value
Age	1.01(0.99−1.04)	0.31
Male sex	1.48 (0.80−2.75)	0.22
ECOG*	1.12 (0.77−1.63)	0.57
BMI	1.04 (1.01−1.08)	0.045
Smoking status	0.85 (0.52−1.39)	0.52
COPD	1.09 (0.60−2.00)	0.77
Hypertension	1.40 (0.90−2.17)	0.13
Neoadjuvant chemotherapy	1.46 (0.88−2.44)	0.14
Preoperative albumin <3.5 g/dl	2.15 (1.28−3.59)	0.004
Robotic approach (vs. open)	0.35 (0.11−1.13)	0.08
Pathologic T stage		
<T2	Ref.	
T2	1.29 (0.74−2.28)	0.43
T3/4	1.10 (0.70−1.74)	0.89
Estimated blood loss	1.00 (1.00−1.00)	0.41

BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; ECOG = Eastern Cooperative Oncology Group.
* 0, 1, 2+.

assessed patients undergoing RC, and this technique requires further study among bladder cancer patients before it can be confidently recommended in this population. Additional techniques including fascial closure using small (5 mm) bites, the use of an abdominal binder, and pre-operative smoking cessation may also be considered to decrease the risk of fascial dehiscence [27,28].

We acknowledge that the present analysis is limited by analysis of a single high-volume referral center, and therefore results may not be generalizable to all practice settings. Due to the relative infrequency of ROR events, only 112 patients with ROR were studied despite an initial cohort of nearly 2,000 patients, leading to insufficient power to detect less robust risk factors for ROR. We also acknowledge the possibility that we failed to capture some events of interest. The time period studied encompassed the initiation of an enhanced recovery after surgery program at our institution, and although the precise impact of this could not be assessed, we notably did not observe an association between year of surgery and ROR. Medication data was not available, and thus the potential impact medications such as immunosuppressants could not be assessed. Prior abdominal surgical history, including organ transplants other than kidney, is likewise not captured in the registry, and therefore was not examined. Preoperative serum albumin levels were missing on nearly a quarter of patients, which could have influenced results; we chose not to exclude these patients due to lack of assurance that data was missing at random. Instead, we imputed missing values and performed models with and without albumin, which did not change our conclusions.

selection bias in choice of approach, our data was insufficient test this hypothesis. Whether a true differential pattern of re-operative complications exists relative to surgical approach requires further investigation.

Prophylactic mesh placement could also be considered to decrease the risk of wound complications, particularly among patients undergoing open RC. A meta-analysis of studies assessing prophylactic mesh placement in midline laparotomies concluded that placement of mesh is associated with an 85% reduction in risk of incisional hernia compared to suture-only closure, although this technique also increased the risks of post-operative seroma and chronic wound pain [26]. However, none of the included studies

Fig. 1. Kaplan-Meier estimates of cancer-specific (A) and overall survival (B), stratified by whether or not the patient experienced a return to the operating room within 90 days of RC.

Despite these limitations, the data reported here are important in examining the usefulness of ROR as a measure of surgical quality among patients undergoing RC. Given our ability to individually review charts to determine reasons for ROR, these data provide a level of detail that is likely not ascertainable from administrative data sets. Whether the observations made here can be corroborated by others, and the degree to which the identified risk factors

Table 4
Multivariable cox proportional hazards analysis of factors associated with death after RC

Feature	Cancer-specific mortality		All-cause mortality	
	Adjusted hazard ratio (95% CI)	*P* value	Adjusted hazard ratio (95% CI)	*P* value
Age	1.01 (0.99−1.02)	0.29	1.02 (1.01−1.03)	<0.001
Male sex	1.16 (0.92−1.45)	0.21	1.29 (1.07−1.57)	0.01
BMI	0.99 (0.97−1.00)	0.15	0.99 (0.97−1.00)	0.06
ECOG*	1.26 (1.07−1.48)	0.01	1.43 (1.26−1.63)	<0.001
Smoker	1.27 (1.03−1.57)	0.03	1.25 (1.05−1.48)	0.01
Albumin <3.5 g/dl	1.00 (0.78−1.27)	0.97	1.04 (0.86−1.27)	0.68
Pathologic T stage				
<T2	Ref.	−	Ref.	−
T2	2.24 (1.72−2.91)	<0.001	1.59 (1.30−1.94)	<0.001
T3/4	4.68 (3.76−5.83)	<0.001	2.91 (2.47−3.43)	<0.001
Node positive	2.46 (2.00−3.04)	<0.001	2.18 (1.81−2.62)	<0.001
Positive margin	1.77 (1.26−2.48)	0.001	1.64 (1.19−2.27)	0.003
Perioperative blood transfusion	1.41 (1.17−1.69)	<0.001	1.34 (1.16−1.56)	<0.001
Return to OR	1.35 (0.98−1.87)	0.07	1.33 (1.01−1.74)	0.04

Also adjusted for history of CAD/MI, PVD, chronic hypertension, diabetes, COPD, acute renal failure, neoadjuvant chemotherapy, adjuvant chemotherapy, diversion type, pathologic CIS, total number of lymph nodes dissected, estimated blood loss.

*ECOG was modeled as a 3-level variable, with categories for 0, 1, and 2+.

for ROR may be modifiable, such as with the use of prehabilitation or differences in surgical technique, requires further study.

5. Conclusion

We observed reoperation in 5.7% of patients following RC, which occurred primarily due to unanticipated postsurgical complications and was associated with an increased risk of all-cause mortality. Identified risk factors for ROR included increasing BMI and preoperative hypoalbuminemia. These data suggest the opportunity for ROR to serve as a quality metric and to be of utility for monitoring process improvement.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urolonc.2018.11.023.

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