

Defining postoperative ileus and associated risk factors in patients undergoing radical cystectomy with an Enhanced Recovery After Surgery (ERAS) program

Connor M. Forbes, MD¹; Ali Cyrus Chehroudi, MD¹; Miles Mannas, MD¹; Andrea Bisailon, BSN²; Tracey Hong, BSN²; Alan I. So, MD¹; Kelly Mayson, MD³; Peter C. Black, MD¹

¹Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada; ²Department of Surgical Services, University of British Columbia, Vancouver, BC, Canada; ³Department of Anesthesiology University of British Columbia, Vancouver, BC, Canada

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See related commentary on page 40

Abstract

Introduction: Postoperative ileus (POI) is a common complication of radical cystectomy (RC), occurring in 1.6–23.5% of cases. It is defined heterogeneously in the literature. POI increases hospital length of stay and postoperative morbidity. Factors such as age, epidural use, length of procedure, and blood loss may impact POI. In this study, we aimed to evaluate risk factors that contribute to POI in a cohort of patients managed with a comprehensive Enhanced Recovery After Surgery (ERAS) protocol.

Methods: A retrospective review of consecutive patients who underwent RC from March 2015 to December 2016 at Vancouver General Hospital was performed. POI was defined a priori as insertion of nasogastric tube for nausea or vomiting, or failure to advance to a solid diet by the seventh postoperative day. To illustrate heterogeneity in previous studies, we also evaluated POI using other previously reported definitions in the RC literature. The influence of potential risk factors for POI, including patient comorbidities, American Society of Anesthesiologists score, gender, age, prior abdominal surgery or radiation, length of operation, diversion type, extent of lymph node dissection, removal date of analgesic catheter, blood loss, and fluid administration volume was analyzed.

Results: Thirty-six (27%) of 136 patients developed POI. Using other previously reported definitions for POI, the incidence ranged from <1–51%. Node-positive status and age at surgery were associated with POI on univariate analysis but not multivariable analysis.

Conclusions: A large range of POI incidence was observed using previously published definitions of POI. We advocate for a standardized definition of POI when evaluating RC outcomes. POI occurs frequently even with a comprehensive ERAS protocol,

suggesting that additional measures are needed to reduce the rate of POI.

Introduction

Radical cystectomy (RC) is a major undertaking for urological patients and surgeons. This 3–8-hour operation¹ has a major complication rate of 4.9–25.5% and a 90-day mortality rate of 2.7%.^{2,3} Postoperative ileus (POI), the delayed return of bowel function after surgery, occurs at a rate of 1.6–23.5% in the RC population.⁴ This rate depends on the definition of POI, which is highly heterogeneous in the literature, making direct comparison across studies difficult.^{4,5} POI is associated with increased length of stay, re-admission, re-operation, and mortality.^{4,6} Preventing POI could potentially reduce the risk of downstream adverse events, so investigation of associated risk factors potentially has major clinical implications.

Previously reported risk factors for ileus post-cystectomy include elevated body mass index and older age.⁴ Some other potential risk factors, including the use of neoadjuvant chemotherapy, were not found to be linked to POI after cystectomy.⁷ However, most reports on POI come from an era that precedes the implementation of formal Enhanced Recovery after Surgery (ERAS) protocols. ERAS protocols are designed to reduce the risk of postoperative complications and to enhance patient quality of life in the perioperative period.^{8,9} ERAS is based on a multidisciplinary approach to standardizing each element of patient care based on the best-available evidence. ERAS protocols guide not only postoperative care, but also preoperative and intraoperative management.

An important focus of ERAS in the context of RC is to prevent POI, which may predispose patients to other complications, increase length of hospital stay, and reduce overall patient experience. For example, bowel edema has been hypothesized to contribute to POI, and goal-directed therapy to optimize intraoperative fluid resuscitation is considered an essential element of ERAS.¹⁰ Epidural anesthesia postopera-

tively is also thought to hasten return of bowel function postoperatively compared to the use of systemic opioids.¹¹ Rectus sheath catheters may increase POI in colorectal surgery, however, data are limited.¹² In this study, we aimed to assess risk factors for ileus after RC in patients managed with a formal, institutional ERAS protocol.

Methods

A retrospective review of charts and data was performed at our institution from March 2015 to December 2016. This included assessment of complications according to the National Surgical Quality Improvement Program (NSQIP), a nationally validated, outcomes-based program to improve quality of surgical care. The start date coincided with a change in the database used for NSQIP data. Ethics approval for this study was obtained from the institutional review board.

Patients were included if they had undergone a RC for bladder cancer in this time period. Patients were excluded if they underwent cystectomy for other indications, such as radiation cystitis. Robotic cystectomies were excluded because there were few of them and they were the initial cases in our institution's robotic cystectomy program.

All patients were managed in the context of a comprehensive ERAS protocol that was launched in our hospital in October 2014 (Appendix; available at cuaj.ca). This protocol included extensive teaching of all healthcare providers involved in the patient journey from the time of surgical booking to time of hospital discharge after surgery. This protocol included a 39-point checklist categorized into nine domains (safety, fall risk/care plan, cognition, assessment, pain management, bowel/bladder, nutrition & hydration, skin/dressings/drains, functional mobility, teaching/discharge planning). Rigorous auditing of adherence to ERAS was conducted in near real-time (monthly), with secondary measures taken to address suboptimal adherence. Outcomes, including length of hospital stay and rates of complications, reported to NSQIP were reviewed quarterly by the multidisciplinary ERAS team.

To define POI as our primary endpoint, we reviewed the literature for previous definitions. Most of the literature focuses on POI after colorectal surgery. Based on the consensus of our multidisciplinary perioperative care team (including nurses, anesthesiologists, general surgeons, and urologists), we settled on an objective and broadly inclusive definition that incorporated elements from many of the published definitions. Ileus, for the purposes of our study, was defined as insertion of a nasogastric tube for nausea, abdominal distension, or vomiting, or failure to advance to a solid diet by the seventh postoperative day.^{2,4} This definition was selected prior to beginning data collection.

We applied six additional definitions of ileus previously reported in the cystectomy literature to our patient data.

These definitions, which are representative of formal definitions used in the RC complication literature, are indicated in Table 1.⁴ The incidence of ileus using each of these definitions was compared.

Demographic data were collected from patient records, including age at surgery, sex, American Society of Anesthesiologists (ASA) score, and history of abdominal surgery or radiation. Surgical variables, including type of urinary diversion, duration of surgery (from nursing record), blood loss (from anesthesia record), and pathological stage were collected. Other perioperative variables were also recorded, including volume of intravenous fluid received at 48 hours and seven days postoperatively, and duration of use of rectus sheath or epidural catheter.

Statistical analysis consisted of initial univariate analysis. Fisher's exact test was used for categorical variables. Shapiro-Wilk testing was applied for normalcy of numeric variables, with t-testing used for normally distributed variables and Wilcoxon-rank testing used for non-normally distributed variables. All variables with a $p < 0.2$ on univariate analysis underwent multivariable analysis.

Results

From March 2015 to December 2016, 136 patients underwent open RC for bladder cancer at our institution. Thirty-six patients (27%) developed POI according to our a priori definition (Fig. 1).

The incidence of ileus was compared using multiple published definitions in the cystectomy literature (Table 1). Incidence ranged from <1% (1/129) to 51% (51/100) for

Table 1. Incidence of postoperative ileus (POI) by definition of ileus used

Definition	Number of patients fulfilling definition	Number of patients with available data	Percentage of patients with POI
NGT placement for nausea/vomiting, or inability to tolerate full diet on POD 7*	36	133	27%
NGT inserted for nausea/vomiting/distension ³	27	133	20%
No BM or flatus on POD 6 ¹¹	1	129	1%
No BM on POD 6	8	126	6%
No BM on POD 4	48	126	38%
Inability to tolerate DAT on POD7 ¹²	33	135	24%
Inability to tolerate DAT on POD 5	51	100	51%

*A priori definition used in this study. BM: bowel movement; DAT: diet as tolerated. NGT: nasogastric tube; POD: postoperative day.

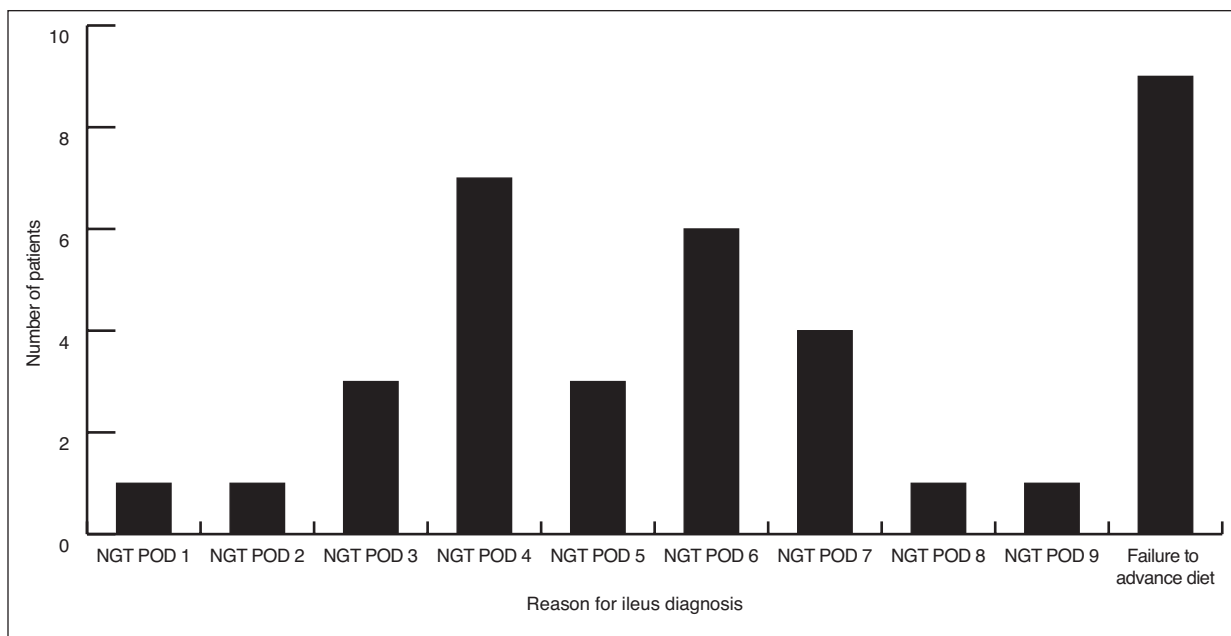


Fig. 1. Number of patients diagnosed with postoperative ileus based on time to nasogastric tube (NGT) placement or failure to advance diet (patient not on a solid diet on postoperative day [POD] 7).

POI, depending on the definition used, with the denominator varying according to available data.

Preoperative, operative, and postoperative variables are summarized in Table 2. The mean age was 67 year (range 36–90) at the time of surgery and 87% (n=115) of the patients were male. Patients with POI were older on average (72 vs. 65 years, $p<0.001$). There were no statistically significant differences in other baseline patient demographics, including comorbidities such as diabetes or inflammatory bowel disease, or preoperative estimated glomerular filtration rate (eGFR).

Most patients (74%, n=98) had an ileal conduit, and the mean operative time was 258 minutes (range 160–453). The standard preoperative analgesia included epidural catheter. For part of the study period, some patients were randomized to receive either an epidural catheter (n=75, 57%) or a rectus sheath catheter (n=57, 43%) in the context of a separate prospective, randomized trial. Twenty-one patients had additional concurrent surgery at the time of cystectomy, including urethrectomy (four patients), nephroureterectomy (four patients), penectomy (two patients), and umbilical hernia repair (two patients). T stage, blood loss, or volume of fluids received perioperatively were not associated with POI.

The variables most strongly associated with POI (according to our definition) on univariable analysis were pathological lymph node positivity ($p=0.02$) and older age at surgery ($p<0.001$). Older patients and those without lymph node metastases had higher rates of POI. Other variables with $p<0.2$ were analgesic catheter type, previous radiation, other surgery performed concurrently, and preoperative eGFR. When these variables were entered into a multivariable

analysis using Wald's test, none remained statistically significant (Table 3). Age at surgery and pathological N stage remained the closest to statistical significance, with $p=0.09$ and $p=0.07$ on multivariable analysis, respectively.

Appendix 1 (available at cuaj.ca) summarizes available adherence data to representative ERAS checklist items at the time of two audits. From the 2014–2016 audit, which covers the study period, $\geq 80\%$ adherence was observed in 7/12 (58%) metrics analyzed. Interestingly, adherence was $<80\%$ for the dietary and mobility metrics postoperatively, which might be expected to impact POI. A subsequent audit in 2019, after the study period, showed a slight improvement to $\geq 80\%$ adherence in 15/23 (65%) analyzed metrics.

Discussion

Postoperative ileus occurs frequently after abdominal surgery and has a major impact on the burden of healthcare costs. For example, in a retrospective cohort of 17 876 colorectal surgery cases in the U.S., the incidence of POI was 17.4%, and the mean additional cost was approximately \$9000 USD for every patient with a POI.¹³ ERAS protocols have been launched widely in an effort to reduce the rate of POI, along with length of hospital stay and other measures of postoperative morbidity.¹⁴ There are 22 items defined in the ERAS Society guidelines for RC, including individual parameters such as omitting preoperative bowel preparation, use of epidural catheter, use of antibiotics, and administration of early oral fluids.^{15–17} Nonetheless, as our data demonstrate, POI remains common (27% of cases) even in the context

Table 2. Demographic and surgical variables, and their association with postoperative ileus

Variable	Ileus	No ileus	p
Total patients	36 (27%)	97 (73%)	N/A
Pre-surgical factors			
Sex			
Male	30 (83%)	85 (88%)	0.57
Female	6 (17%)	12 (12%)	
Mean age at surgery (range)	72 (49–86)	65 (36–90)	<0.001*
Diabetes			
Yes	7 (5%)	15 (11%)	0.6
No	29 (22%)	82 (62%)	
Inflammatory bowel disease			
Yes, on treatment	0	0	0.45
Yes, no treatment	3 (8%)	5 (5%)	
No	33 (92%)	92 (95%)	
Previous abdominal surgery			
Yes	11 (31%)	32 (33%)	0.84
No	25 (69%)	64 (67%)	
Previous radiation			
Yes	5 (14%)	5 (5%)	0.14
No	31 (86%)	91 (95%)	
Neoadjuvant chemotherapy			
Yes	8 (22%)	31 (32%)	0.29
No	28 (78%)	65 (68%)	
Mean Preoperative eGFR (ml/min/1.73 m ² , range)	67 (33–98)	73 (13–127)	0.19
Operative factors			
Mean operative time (min, range)	253 (160–358)	261 (160–453)	0.77
Type urinary diversion			
Ileal conduit	30 (83%)	68 (70%)	0.42
Studer neobladder	5 (14%)	24 (25%)	
Indiana pouch	1 (3%)	2 (2%)	
Other	0	3 (3%)	
Pelvic lymph node dissection			
None	0 (0%)	3 (3%)	0.56
Standard	26 (72%)	61 (63%)	
Extended	10 (28%)	33 (34%)	
Other surgery performed concurrently			
Yes	3 (8%)	18 (19%)	0.19
No	33 (92%)	79 (81%)	
Estimated blood loss >500 mL			
Yes	18 (51%)	48 (53%)	
No	17 (49%)	42 (47%)	
Estimated blood loss (ml, range)	747 (200–2500)	797 (150–3000)	1
Intraoperative crystalloid (mean mL, range)	3044 (1400–5400)	3037 (900–6000)	0.9
Analgesia catheter type			
Epidural	24 (67%)	51 (53%)	0.39
Rectus sheath	12 (33%)	45 (47%)	
Abdominal or pelvic drain inserted			
Yes	34 (94%)	90 (95%)	1
No	2 (6%)	5 (5%)	

*Statistically significant. ASA: American Society of Anesthesiologists Score; eGFR: estimated glomerular filtration rate; POD: postoperative day; SBP: systolic blood pressure.

Table 2 (cont'd). Demographic and surgical variables, and their association with postoperative ileus

Variable	Ileus	No ileus	p
Total patients	36 (27%)	97 (73%)	N/A
Postoperative factors			
Pathological T stage			
T0/Ta/Tis/T1	17 (47%)	44 (45%)	0.85
T2/T3/T4	19 (53%)	53 (55%)	
Pathological N stage			
N0	32 (89%)	66 (68%)	0.02
N1/N2/N3	4 (11%)	29 (32%)	
Transfused in first 48 hours			
Yes	12 (36%)	25 (28%)	0.38
No	21 (64%)	65 (72%)	
Mobilized once POD 0–1			
Yes	14 (51%)	46 (61%)	0.5
No	13 (49%)	30 (39%)	
Full fluids started on POD#1			
Unrestricted	0	6 (6%)	0.14
Restricted (<500 ml)	20 (57%)	63 (66%)	
No	15 (43%)	27 (28%)	
Patient hypotensive on the ward (SBP <90)			
Yes	6 (18%)	12 (13%)	0.57
No	28 (82%)	82 (87%)	
First 48 hours fluid (mean mL, range)	10121 (6711–13932)	9858 (5888–28973)	0.14
Analgesic catheter remove day postoperative (mean days, range)	3.8 (2–8)	3.4 (1–6)	0.3

ASA: American Society of Anesthesiologists Score; eGFR: estimated glomerular filtration rate; POD: postoperative day; SBP: systolic blood pressure.

of a formal, comprehensive ERAS protocol that has strong multidisciplinary institutional support with frequent rigorous auditing.

The definitions of ileus in the literature are variable. Previous studies of POI after RC have used definitions based on the time to first flatus, bowel movement, or diet as tolerated (DAT), insertion of a nasogastric tube, or vomiting requiring cessation of oral intake.⁴ Interestingly, in a review of POI after cystectomy, 56/77 included studies did not include a specified definition of ileus and relied instead on a clinical diagnosis.⁴ We analyzed the studies that had a specific,

Table 3. Multivariable analysis for variables associated with postoperative ileus with p>0.2 on univariate analysis

Variable	Reference variable	p
Analgesic catheter type	ref=epidural	0.15
Previous radiation	ref=no	0.46
Pathologic N stage	ref=N0	0.07
Other surgery performed concurrently	ref=no	0.2
Age at surgery	N/A	0.09
Preoperative eGFR	N/A	0.56
Fluid in the first 48 hours	N/A	0.27

eGFR: estimated glomerular filtration rate.

reproducible definition of ileus and selected our outcome definition a priori before beginning data collection. Other representative definitions from the literature were also applied to our data to compare POI incidence. We found great variability in the incidence of POI depending on definition, ranging from 1% if defined by absence of flatus and bowel movement on the sixth postoperative day, to 51% if defined by DAT on the fourth postoperative day. The limitation of using first flatus, bowel movement, or DAT in the definition of ileus is the potential for any one of these to be realized early in the postoperative course, but followed later by typical signs and symptoms of POI. For example, patients may be started empirically on a solid diet immediately after surgery only to require a nasogastric tube for nausea and vomiting days later. On the other hand, our definition relies, in part, on the subjective clinical decision to insert a nasogastric tube, which may be placed liberally by different providers and at different centers. There has been difficulty finding a consensus definition for ileus,⁵ and it may not be appropriate to have the same definition for all surgeries. However, this study helps to illustrate the large variability in POI incidence depending on definition used.

We analyzed the risk factors for POI in a cystectomy population managed with an ERAS protocol. The two factors predictive of POI on univariate analysis were age at surgery and pathological nodal involvement ($p < 0.001$ and $p = 0.02$, respectively). However, neither of these remained statistically significant on multivariable analysis. Mean age was 72 for those patients who developed POI, compared to 65 for those patients who did not develop POI. Previous studies have found an association between age and POI after RC.⁷ The reason for this observed age dependence of POI is unknown, but proposed mechanisms include decreased mobility, decreased tolerance for the side effects of opioid medications, and decreased motility of the bowels at baseline.⁷

The absence of nodal metastasis (pN0 vs. pN1–3) was statistically significant for association with POI on univariate analysis ($p = 0.02$), but did not retain significance on multivariable analysis. This association would be difficult to explain, since one would postulate the opposite, whereby an increase in severity of disease or a more extensive lymph node dissection might result in a higher rate of POI. In our study, as well as in prior studies, the extent of lymph node dissection did not predict ileus.^{18,19} A recent, randomized, controlled trial from Germany found no difference in recurrence-free or overall survival with an extended lymph node dissection compared to a limited lymph node dissection.²⁰ Of note in that study, ileus incidence (which was not explicitly defined) was comparable between groups. POI occurred in 22/190 (12%) limited lymph node dissection patients and 14/173 (8%) extended lymph node dissection patients.

The mean time to removal of epidural or rectus sheath catheters for patients who developed POI was 3.8 days

compared to 3.4 days for the non-POI patients ($p = 0.3$). The occurrence of POI could itself affect duration of use of an analgesic catheter, so that we cannot conclude that a longer duration of indwelling analgesic catheter causes POI. In a Cochrane review, patients with epidural catheters have been found to have reduced time to return of normal gastrointestinal function, duration of hospital stay, and pain after abdominal surgery compared to patients without epidural catheters.²¹ A small study comparing rectus sheath to epidural catheter for return of bowel function did find a statistically significant higher incidence in ileus in the rectus sheath group, but the absolute numbers were too small to be widely generalizable.¹⁴ Our study did not find an association between type of analgesic catheter and incidence of POI.

A noteworthy negative finding is that intravenous fluid administration, both intraoperatively and in the first 48 hours, was not associated with ileus. A small, randomized, controlled trial found that time to postoperative return of bowel function was reduced with restricted intravenous fluid and salt administration.²² The authors hypothesized that reduced gastrointestinal edema could explain this finding. Another randomized study found that a restrictive intraoperative hydration protocol coupled with a norepinephrine infusion resulted in a lower complication rate and a shorter hospital stay.²³ However, shortened hospital stay was not replicated in a different study in colorectal patients,²⁴ and our study also did not find an association. Our series may lack the power to discern differences based on fluid volumes, especially since all patients were managed with the intent of restricting fluids despite differences in volume.

Previous radiation and concurrent performance of another surgery at the time of cystectomy were not associated with POI in this study. Radiation might be suspected to have an association with ileus by obliteration of surgical planes and reduced tissue healing. However, complication rates, including ileus, have not been found to have an association with radiation in a study including 846 patients.²⁵ Likewise, the performance of another surgery at the time of cystectomy increases operating room time and potentially increases bowel manipulation, but was not found to have an association with ileus for our study. This is possibly because the types of additional surgery were often not intra-abdominal (e.g., penectomy, urethrectomy) and, therefore, might have only a minor impact on bowel function.

An important conclusion of our study is that we need to continue to identify new means to reduce the rate of POI after cystectomy and, thereby, improve patient outcomes. Alvimopan and N-methylnaltrexone are peripheral mu-opioid receptor antagonists that represent an important advance in perioperative care.²⁶ The evidence for N-methylnaltrexone in the setting of RC is very limited,²⁷ but one multi-institutional, randomized, controlled trial has evaluated the impact of alvimopan on the return of bowel function after cystectomy

in 277 patients managed without a formal ERAS protocol.^{26,28} Those patients who received alvimopan for seven days postoperatively had statistically significant reduced need for nasogastric tube insertion postoperatively (24.6% vs. 7.7%, $p < 0.001$).²⁶ Although the definition differs between studies, the non-alvimopan group had a similar incidence of nasogastric tube insertion as POI in our study, while the alvimopan group was greatly improved. There were also significant improvements in time to solid food intake, length of stay, major adverse events, and POI-related morbidity.²⁶ This was designated as moderate-quality evidence supporting alvimopan's use for RC.²⁸ It is important to emphasize, however, that these patients were not managed with a formal ERAS protocol, so it remains uncertain whether alvimopan would have the same impact in an ERAS cohort. Alvimopan has not been approved in Canada and was not available for use in our patient cohort.²⁹

Limitations

This study has several limitations. Firstly, the study is observational in nature, which precludes randomization and reduces the level of evidence. The study was also at a single, tertiary academic center. Local practice and referral patterns, which were not captured in our data and analysis, may limit the generalizability of the findings to other cystectomy populations. A multi-institutional approach would have yielded more generalizable results, and this is something to consider for future studies. The small sample size limits the power of the analysis, and it is possible that a greater number of patients would have resulted in statistical significance for one or more of the tested variables. In addition, greater numbers would have allowed for the use of advanced statistical techniques, such as propensity score-matching, which can counteract confounders even in studies lacking a control group. Noteworthy strengths of the study include the prospective collection of most of the data, including the adherence to individual components of the ERAS protocol, and the granularity of data available, such as intraoperative fluid resuscitation. While this study did not include robotic approaches, future studies could also examine the impact of newer robotic approaches on POI after cystectomy in the Canadian population.

Conclusions

POI remains a common complication after RC, even when patients are managed with a comprehensive ERAS protocol. The incidence of POI after RC varies greatly depending on definition of POI used. In this retrospective review, age and pathological nodal involvement were found to be associated with POI on univariate, although not multivariable, analysis. This may help identify patients at higher risk for POI. More

research needs to be conducted to further reduce the rate of POI after RC in the setting of comprehensive ERAS.

Competing interests: Dr. So has been an advisory board member for AbbVie, Amgen, Astellas, Bayer, Janssen, Ferring, and TerSera; and has participated in clinical trials supported by Astellas, Ferring, and Janssen. Dr. Black has attended advisory boards for AbbVie, Amgen, Astellas, Biocancell, Cubist, Janssen, Novartis, and Sitka; has been a speaker for AbbVie, Janssen, Ferring, Novartis, and Red Leaf Medical; has received grants/honoraria from Pendopharm; has participated in clinical trials supported by Amgen, Astellas, Ferring, Janssen, and Roche; and has received research funding from GenomeDx, iProgen, Lilly, and New B Innovation. The remaining authors report no competing personal or financial interests related to this work.

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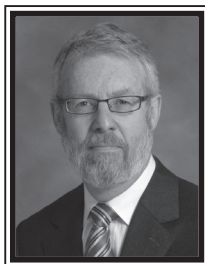
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Correspondence: Dr. Connor M. Forbes, Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada; cmforbes@alumni.ubc.ca

Michael A.S. Jewett is awarded THE ORDER OF CANADA



Dr. Michael A.S. Jewett has recently been announced as a recipient of the Order of Canada for his life-saving innovations in surgical oncology and for his advocacy of patient-centered clinical care.

Dr. Jewett is a professor of surgery (urology) at the Princess Margaret Cancer Centre and at the University of Toronto, where he held the Farquaharson Clinical Research Chair in Oncology. He is a member and has served in leadership roles and received awards from many cancer and urological associations, including the International Society of

Urology, the Society of Urologic Oncology, the American Society of Clinical Oncology, the American Urological Association, and the Canadian Urological Association, for which he served as President in 2005 and was awarded a lifetime achievement honor in 2011. In 2017, he was awarded the Canadian Cancer Research Alliance Award for Exceptional Leadership in Patient Involvement in Cancer Research. He has been a visiting professor or speaker in over 30 countries at over 100 institutions; has held multiple research grants; and has published more than 400 scientific papers, book chapters, and articles.

The founder and immediate past-Chair of the Kidney Cancer Research Network of Canada and currently the Co-Chair of the NCI renal task force, Dr. Jewett has had a long interest in many aspects of kidney cancer research, patient care, and knowledge transfer.

Please join the Canadian urological community in congratulating Dr. Jewett on this well-deserved recognition.

