

Radical Cystectomy Perioperative Care Redesign



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OBJECTIVE	To present an evidence-based review of the perioperative management of the radical cystectomy (RC) patient in the context of a care redesign initiative.
METHODS	A comprehensive review of the key factors associated with perioperative management of the RC patient was completed. PubMed, Medline, and the Cochrane databases were queried via a computerized search. Specific topics were reviewed within the scope of the three major phases of perioperative management: preoperative, intraoperative, and postoperative. Preference was given to evidence from prospective randomized trials, meta-analyses, and systematic reviews.
RESULTS	Preoperative considerations to improve care in the RC patient should include multi-disciplinary medical optimization, patient education, and formal coordination of care. Efforts to mitigate the risk of malnutrition and reduce postoperative gastrointestinal complications may include carbohydrate loading, protein nutrition supplementation, and avoiding bowel preparation. Intraoperatively, a fluid and opioid sparing protocol may reduce fluid shifts and avoid complications from paralytic ileus. Finally, enhanced recovery protocols including novel medications, early feeding, and multi-modal analgesia approaches are associated with earlier postoperative convalescence.
CONCLUSION	RC is a complex and morbid procedure that may benefit from care redesign. Evidence based quality improvement is integral to this process. We hope that this review will help guide further improvement initiatives for RC. UROLOGY 86: 1076–1086, 2015. © 2015 Elsevier Inc.

THE NECESSITY OF CARE REDESIGN

Novel reimbursement models are on the horizon as a result of the Affordable Care Act. Bundled payments, value-based payments, and accountable care organizations represent a significant change from traditional fee-for-service payment modeling. In the United States, expansion of these programs to urologic oncology procedures may impact delivery of care as reimbursement may be tied to outcomes.

A proactive attempt at reducing postoperative complications, improving outcomes, and preventing unplanned readmissions will be essential in this new payment landscape. The key to successful navigation of these changes will be improved efficiency in the delivery of care rather than restricting resources. Thus, to balance quality measures, oncological outcomes, and patient satisfaction, a comprehensive *care redesign* process is the ideal method to harmonize physician values and patient needs in the modern

context of limited resources. The redesign process involves an intentional effort to standardize and improve patient care by reducing complications and mitigating risks. These efforts center on the use of guidelines, best practices, evidence-based medicine, and improved efficiencies.

Radical Cystectomy (RC)

RC is associated with a high frequency of complications because of the complex nature of the surgery and a patient population with frequent comorbidities. Current or prior smokers comprise 80% of RC patients, and smoking itself contributes to both developing and dying from bladder cancer.¹ Thirty- and 90-day complication rates from a prospectively collected database using a modified Clavien system were 58% and 64%, with 79% experiencing “minor” (grade 1 or 2) complications only and 13% experiencing “major” (grades 3–5) complications.² Ninety-day mortality rates between 2.7% and 9% have been reported.^{2,4} The average length of stay (LOS) after RC and readmission rates vary considerably between centers, and adverse events or complications following RC have been linked to increased LOS, in-hospital mortality, and costs.^{5,6} Reimbursement remains neutral for bladder cancer diagnosis related groups and will most likely decrease over the next several years. Thus, there is significant room and need for improvement in bladder cancer care. A multidisciplinary approach at every stage of patient care from preoperative

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patient counseling to postoperative follow-up will be necessary.

METHODS

We performed a comprehensive review of the key factors associated with perioperative management of RC. A computerized search was undertaken using PubMed, Medline, and the Cochrane database for a variety of Medical Subject Headings terms and free text phrases encompassing the variety of topics included in this review from January 1, 2000 to the present date. Seminal manuscripts outside of this range were included if they remained pertinent.

Depending on the topic, varying levels of evidence are included in this review, with the highest level of evidence used when possible. Preference was given to prospective randomized trials, meta-analyses, and systematic reviews. The reference lists of identified articles were additionally assessed. A full review of search terminology, results, and notes can be found in the Supplementary Data. Descriptions of trials and strength of evidence are included where possible.

RESULTS

Preoperative

Patient Education. Appropriate counseling and teaching are an essential component of care redesign and are known to improve outcomes and decrease patient anxiety.⁷ Prospective studies in intensive preoperative ostomy teaching prior to colorectal surgery compared with traditional postoperative teaching improves time to stoma proficiency (5.5 vs 9 days, $P < .001$), shortens LOS (8 vs 10 days, $P = .03$), lowers the frequency of unplanned interventions per patient (median 0 vs 0.5, $P = .03$), and lowers cost ($-\$2104/\text{patient}$).⁸ A review of 5 studies determined that health-related quality of life metrics also improved with preoperative stoma siting and education.⁹

Clean intermittent catheterization (CIC) teaching prior to neobladder diversions may also be considered, as voiding failure is a potential postoperative issue that can lead to infectious and obstructive complications, resulting in morbidity and patient frustration. In a series of 19 female patients undergoing neobladder diversion, 7 (36.8%) required CIC at least temporarily, all of which were attributed to the development of neocystoceles.¹⁰ In a prospective study of urinary functional outcomes after neobladder diversion, 17 of 179 patients required CIC, with 6 (35.2%) considering it a moderate or large bother.¹¹ A retrospective analysis of 231 males with neobladder creation found a long-term need for CIC in 10 (4.3%).¹² Preoperative CIC teaching has the added benefit of improving patients' ability to perform irrigation of mucus. Further, preoperative pelvic floor strengthening exercises similar to those performed prior to radical prostatectomy may benefit RC patients' continence with neobladder reconstruction.

Currently, no prospective evidence exists that assesses the benefits of patient education on outcomes after RC.

However, a meta-analysis of 19 studies in general surgery had equivocal findings on improved postoperative outcomes but demonstrated that patients retained the information taught to them.¹³ Several institutions have begun using multimedia tools (websites, videos) and intensive verbal and written personal counseling about expectations and goals of perioperative RC care. As these interventions have virtually no potential for detriment, they should be included in any care redesign program and further studied for efficacy. Tools such as the "Urostomy Education Scale" have been developed to assess patient knowledge and abilities with regard to stoma care and can be integrated into patient education efforts.¹⁴

Coordination of Care and Disposition. The timing of hospital discharge and postoperative placement is a challenge for RC patients. Further compounding this issue is that RC care involves many providers. Care coordinators or care navigators have been shown to improve patient safety and quality of care by helping with healthcare access and literacy. Care navigators' integration into routine cancer care has been explored by the National Cancer Institute's Patient Navigation Research Program.¹⁵ Navigators are known to add modest cost to care,¹⁶ but the true overall cost savings potential of navigators in preventing complications, decreasing LOS, and reducing readmissions is considerable.

As mentioned, RC patients have high risk for readmission and out-of-hospital complications. Risk stratifying patients prior to their operation may aid in placement, prevent readmissions, and improve mortality.¹⁷ Further, postdischarge "phone interventions" performed by nurses or care navigators are now being explored as a means of preventing readmissions by early identification of problematic symptoms.

"Prehab"—Nutritional Status and More. Preoperative nutritional status is recognized as a potentially modifiable risk factor for perioperative complications and mortality.^{18,19} Although malnutrition can be defined by several objective and subjective variables, determinations based on body mass index, involuntary weight loss, or serum albumin levels are common. Serum albumin levels less than 4 g/dL were an independent predictor of postoperative RC complications, need for more acute postoperative home care, and mortality in several studies.^{17,19,20}

Attempts at objectively defining malnutrition have led to the use of computed tomography radiographic determinations of sarcopenia, or severe wasting of skeletal muscle. This definition of malnutrition was shown to be associated with an increased risk of bladder cancer death (hazard ratio [HR] 2.14, $P = .007$) and all-cause mortality (HR 1.93, $P = .004$) after RC and superior to commonly used performance (Eastern Cooperative Oncology Group) and comorbidity scores (Charlson) in risk assessment in a retrospective study.²¹

The importance of optimizing nutrition and the time necessary to do so must be balanced with the need for expeditious surgery or neoadjuvant chemotherapy. The benefit

of short term preoperative nutritional support prior to RC is currently being studied (Clinicaltrials.gov Identifier: NCT01868087). The goal is to translate the improvements seen prior to GI surgery that was determined by a Cochrane review. Preoperative immune enhancing nutrition, which is oral supplementation with added nutrients (typically glutamine, alanine, omega-3 fatty acids), was found to have a positive influence on postoperative complications (HR 0.61, 95% confidence interval [CI] 0.44-0.84; HR 0.67, 95% CI 0.51-0.89), infectious complications (HR 0.51, 95% CI 0.31-0.84; HR 0.43, 95% CI 0.27-0.70), and hospital LOS (-1.2 day, 95% CI -1.89 to -0.14 day; -2.59 days, 95% CI -3.66 to -1.52) when compared with both standard nutritional support and no nutritional support, respectively. When preoperative parenteral nutrition was compared with no nutritional support, improved rates of major complications (HR 0.64, 95% CI 0.46-0.87) without change in infectious complications (HR 0.94, 95% CI 0.80-1.10) were identified in GI surgery patients.²² Considering LOS, preoperative immune enhancing nutrition compared with control or standard nutrition was associated with an approximately 1 day decreased LOS (-1.01 day, $P = .02$) and an even greater decreased LOS (-2.59, $P < .001$) when compared with no nutrition. There was no difference seen in LOS when comparing preoperative standard oral nutrition with no nutrition.²²

Preoperative smoking cessation and alcohol abstinence also positively influence outcomes. A systematic review including 11 randomized control trials (RCTs), including genitourinary surgeries, found reduced risk of complications (relative risk [RR] 0.56, 95% CI 0.41-0.78, $P < .001$) in patients who stopped smoking prior to surgery.²³ Similar postoperative benefits were seen in an RCT of "alcohol misusers" without liver disease who abstained from alcohol 1 month prior to elective colorectal surgery. Improvements in overall complication rates (31% vs 74%, $P = .02$) and lower rates of myocardial infarction and arrhythmias (23% vs 85%) were demonstrated.²⁴

Bowel Preparation (BP). BP has historic roots in colorectal surgery and was adapted by urologists without appropriate investigation. BP typically includes either a mechanical bowel preparation (MBP) or an antibiotic bowel preparation with the goal of reducing bacterial load in the bowel and preventing complications. Questions regarding the efficacy of BP in preventing complications and the potential for harm secondary to its use have been raised.²⁵ In the colorectal literature, a large RCT,²⁶ a systematic meta-analysis,²⁷ and a Cochrane review²⁸ have cast doubt on the benefit of BP in preventing postoperative complications or improving hospital LOS. In the urology literature, 6 studies assessed the effect of BP on outcomes in RC. All studies involved the exclusive use of ileum for urinary diversion. Table 1 displays a summary of the 6 studies; 2 of which compared MBP with no MBP,^{29,30} whereas the other 4 compared antibiotic bowel preparation + MBP and no BP.³¹⁻³⁴ A systematic review and meta-analyses have been completed with similar findings to our compilation.^{35,36} At

this time, there does not appear to be an evidence-based benefit of BP prior to cystectomy. Further, there may be both a patient satisfaction benefit to no BP and a decreased need for intraoperative resuscitation from cathartic dehydration.

Carbohydrate Loading (CL). Recent evidence has questioned the benefits of preoperative fasting. Overnight starvation may alter metabolism and lead to dehydration.³⁷ Further, a depleted carbohydrate reserve combined with the metabolic stress of surgery has been shown to cause transient insulin resistance during the postoperative period, which is linked to poorer outcomes.³⁸ CL mitigates these effects, as a 2-hour load prior to surgery decreases insulin resistance and subjectively improves patient anxiety, hunger, and thirst.³⁷ Protein stores are preserved and strength is improved, leading to better physical therapy and rehabilitation. A Cochrane review of 22 RCTs further demonstrated safety, with no reduction in gastric emptying or complications for patients allowed clear fluids up to 2 hours before surgery as opposed to midnight.³⁷ A recent meta-analysis demonstrated improved insulin resistance, no aspiration events, and a reduced overall LOS (-1.08 day [-1.87 to -0.29 day], $P = .007$) in patients undergoing major abdominal surgery who got CL vs control (fasting or placebo).³⁹ A subsequent Cochrane review of 27 studies, 18 of which examined elective major abdominal surgery, found evidence of reduced LOS (mean difference -1.66, 95% CI -2.97 to -0.34) in CL vs fasting or placebo and no influence on postoperative complications (RR 1.00, 95% CI 0.87-1.16).⁴⁰ Further prospective studies, specifically within RC, are needed.

Intraoperative

Intraoperative Anesthesia Concerns and Fluid Sparring. Intraoperatively, prevention of hypothermia, and antibiotic and thromboembolism prophylaxis is considered standard of care. Core temperature should be maintained $>36.0^{\circ}\text{C}$ to prevent wound infections, coagulopathy, and myocardial ischemia, as well as reduce hospital LOS.⁴¹ Goal-directed fluid therapy optimizes oxygen delivery and perfusion by maintaining physiological euvolemia. Excess administration of intravenous fluids can lead to pulmonary complications and bowel edema that contributes to impaired motility and postoperative ileus (POI).⁴² Conversely, volume depletion can cause end-organ hypoperfusion and lead to morbidity and GI dysfunction as well.⁴³ Recently, an RCT in RC was conducted utilizing a restrictive intraoperative fluid administration group vs a standard fluid administration group. In the restrictive group, 1-3 mL/kg/h of crystalloid fluid was infused throughout the case with the addition of a norepinephrine infusion (2 $\mu\text{g/kg/h}$ titrated up to 8 $\mu\text{g/kg/h}$) to maintain mean arterial pressures between 60 and 100 mmHg. The total volume infused during surgery was 1700 mL vs 4300 mL crystalloid between the 2 groups ($P < .0001$) after 190 cases. Improved outcomes in terms of POI (0% vs 10%, $P = .0006$), any postoperative complication (RR 0.7; 95% CI 0.55-0.88, $P = .006$), and hospital LOS (15 vs 17 days, $P = .01$) were seen.⁴⁴ Further review of these data suggest that ju-

Table 1. Bowel Preparation

Author	Year	Patients (n)	Study Design	Cohorts	Surgery Type	Length of Stay (Median)	Complications	Abdominal or GI Complications	Diet and Bowel Function Outcomes
Large et al	2012	180	Retrospective case series	MBP (n = 105) vs no MBP (n = 75)	RC with NB + IC	8 vs 9 days, $P = 0.4$	Qualitatively described as nonsignificant	Clavien grade 3-5: 3: 6.7% vs 14.7%, $P = 0.08$	Tol general diet: 7 vs 6 days, $P = 0.7$
Hashad et al	2012	40	Prospective RCT	MBP + ABP (n = 20) vs no BP (n = 20)	RC with NB + CP + IC	Not included	Overall: 55% vs 35%, nonsignificant	POI: 2 vs 1 patient, nonsignificant	Not included
Xu et al	2010	86	Prospective RCT	MBP + ABP (n = 47) vs no BP (n = 39)	RC with IC	14.5 vs 15.7 days, $P = .46$	SSI: 6.4% vs 5.1%, $P = .59$	Leak: 2.1% vs 2.6%, $P = .7$, POI: 2.1% vs 5.1%, $P = .43$	Tol oral diet: 4.8 vs 5.4 days, $P = .52$
Raynor et al	2010	70	Retrospective case series	MBP (n = 37) vs no MBP (n = 33)	RARC and ORC with NB + IC	5.2 vs 5.1 days, $P = .8$	Overall: 32.4% vs 42.4%, $P = .395$	21.6% vs 15.1%, $P = .494$	Flatus: 2.6 vs 2.4 days, $P = .326$; BM: 3.6 vs 3.4 days, $P = .285$
Tabibi et al	2007	62	Prospective nonrandomized	MBP + ABP (n = 30) vs no BP (n = 32)	RC with NB + CP + IC	17.5 vs 17 days, $P = .54$	Total: 2 vs 4, $P = .69$	Fistula or peritonitis: 1 vs 0, $P = 1.0$	Tol oral diet: 5 vs 5 days, $P = .29$
Shafii et al	2002	86	Retrospective case series	MBP + ABP (64) vs no BP (22)	RC with IC	31.7 vs 22.8 days	SSI: 7 vs 3 patients	POI: 21 vs 1 patient; fistula: 7 vs 2 patients	Tol oral fluids: 5.8 vs 3.4 days

ABP, antibiotic bowel preparation; BP, bowel preparation; CP, continent pouch urinary diversion; IC, ileal conduit urinary diversion; MBP, mechanical bowel preparation; NB, neobladder urinary diversion; ORC, open radical cystectomy; POI, postoperative ileus; RARC, robotic-assisted laparoscopic radical cystectomy; RC, radical cystectomy; RCT, randomized control trial; Tol, toleration of. Abdominal or GI complications: bowel leak, peritonitis, abdominal abscess, fistula, small-bowel obstruction, hernia, and dehiscence.

dicious administration of intravenous fluids may also improve erectile function (79% vs 48% of patients retained similar levels of preoperative erections, $P = .002$), improve daytime continence (86% vs 64%, $P = .016$), and reduce the need for blood transfusion intraoperatively (8% vs 31%, $P < .0001$) and postoperatively (28% vs 48%, $P = .016$).⁴⁴⁻⁴⁶

Postoperative

Enhanced Recovery Protocols (ERPs). The goal of ERPs is to return patients to their baseline functional status soon after surgery with attention to diet, ambulation, pain control, and earlier return of bowel function. ERPs are an essential component of the redesign process as they improve objective outcomes and influence patient satisfaction and health-related quality of life metrics.⁴⁷ ERPs are not without complexity, as most protocols have been described to have up to 22 essential elements (Fig. 1).⁴⁸ The reason for improvements in these protocols is difficult to attribute to a single intervention and have been described as “an aggregate of marginal gains.”⁴⁹

There have been several prospective ERP trials for RC. Daneshmand et al⁵⁰ reported their experience for more than a year with 126 consecutive RC patients. LOS was decreased to a median of 4 days (range 3-15 days) from a prior matched cohort median of 8 days ($P < .001$). Median time to bowel movement (BM) and toleration of general diet was 2 days (BM: range 1-6 days, general diet: range 1-5 days). Other RC ERPs have been established at other institutions with similarly improved outcomes, a full description of which can be found in Table 2.

Radical Cystectomy ERP Components

Preoperative counseling and education
 Preoperative medical optimization
 Absence of Bowel Preparation
 Carbohydrate Loading
 Reducing Preoperative Fasting
 VTE prophylaxis
 Multi-modal Postoperative pain control
 Appropriate Antimicrobial prophylaxis
 Established Anesthesia Protocol
 No NG tube
 Postoperative Ileus Prevention
 Postoperative Nausea/Vomiting prophylaxis
 Early Mobilization
 Early Feeding
 Audit

Figure 1. The recommended components to consider for inclusion in an enhanced recovery protocol. (Adapted from Cerantola et al,⁴⁸ used with permission.)

Further advantages of ERPs are reduction in variability of care, which improves outcomes as these pathways provide the opportunity to standardize processes and problem solving, and eliminate inconsistency. The result is that in every aspect of the delivery of care, there exist clear expectations and demonstrated capabilities. Though situational change is a constant in the healthcare environment, process standards must be applied in all applicable areas to reduce the controllable variances and ensure regulatory compliance, patient and staff satisfaction, and outcomes. Through these standardized pathways or programs, we are able to establish a confidence in ourselves, our peers, our patients, and our families that what we say will indeed occur.

In addition to previously reviewed bowel preparation and opioid-sparing analgesia, select hallmarks of ERP include the use of promotility agents, early removal of nasogastric tube (NGT), opioid sparing analgesia, and gum chewing, which will be reviewed separately below.

Postoperative Pain Control. Significant controversy exists on the best approach to postoperative pain control. Epidural anesthesia (EA) has been used to reduce the use of systemic narcotics. Intraoperative neuraxial or regional anesthesia techniques has been demonstrated to minimize perioperative opiate administration and expedite recovery in a Cochrane review.⁵¹ However, there are concerns about the potential for excess intraoperative and postoperative fluid administration secondary to venodilation with EA.²⁵

Thoracic EA hastens return of bowel function when compared with patient-controlled analgesia (PCA) with opiates following open colorectal surgery in a prospective randomized trial. Time to GI-2 recovery, defined as toleration of solid food and first BM, was shorter (3.1 ± 1.7 days vs 4.6 ± 1.6 days; $P < .01$) in the epidural group compared with the PCA group.⁵² Thoracic epidural likely offers less benefit to laparoscopic procedures and can lead to excessive fluid administration in minimally invasive surgery as well.⁵³

Recently, the use of transversus abdominis plane (TAP) block has been advocated as an alternative analgesic technique perioperatively.⁵⁴ Only limited evidence supports that single-administration TAP block, plus multimodal analgesia, is effective in reducing pain scores and opioid use after abdominal surgery. Recent studies have compared EA with TAP with intermittent bolus doses, finding no significant advantage of EA.⁵⁵ Compared with PCA alone, continuous TAP block resulted in lower postoperative pain scores and less use of rescue narcotics in a prospective study.⁵⁶

In a more recent randomized trial, continuous TAP catheter use was compared with EA for postoperative pain control after abdominal surgery. Patients in the epidural group received a bolus of 8-15 mL of ropivacaine 0.2% and an infusion of 5-15 mL/h and the TAP block group received a bolus dose of 20 mL ropivacaine 0.375% bilaterally and an infusion of 0.2% ropivacaine 8/mL/h bilaterally, for 3 days. Both groups received intravenous paracetamol and breakthrough pain was controlled via fentanyl PCA.

Table 2. RC ERPs

Author	Year	Total Patients (n)	Study Design	Cohorts	Surgery*	Results of Primary Outcomes	Results of Secondary Outcomes
Dutton et al [†]	2014	165	Retrospective	ERP	ORC	All patients' median LOS: 10.5 days All patients' complication rates: POI (21.2%), UTI (8.5%) All patients' readmissions: 14% All patients' mortality rate: 1.2%	Subgroup median LOS: 8 days Subgroup time to BM: POD6 Subgroup full mobilization: POD2
Smith et al	2014	133	Retrospective	non-ERP (n = 69) 1st stage ERP (n = 37) 2nd stage ERP (n = 27)	ORC	Median LOS: 14, 10, 7 days ($P < .0001$) 30-day readmission rate: 7.2%, 10.5%, 18.5% ($P = .27$) Clavien grade >2 complications: 11.6% vs 8.1% vs 14.8% ($P = .28$)	Median time to flatus: 5, 5, 4 days ($P = .08$) POI rate: 45% vs 30% vs 15% ($P = .017$) Reoperation rate: 11.6% vs 7.9% vs 8.7% ($P = .76$)
Daneshmand et al ^{‡50}	2014	110	Retrospective	ERP (n = 110) Matched cohort	RC	Median LOS (ERP vs matched control): 4 vs 8 days ($P < .001$)	Median time to flatus and/or BM: 2 days 30-day mortality: 1% 30-day readmission: 21% 30-day complications: 65%
Karl et al ^{§61}	2014	101	Prospective	Traditional management (n = 39) ERP (n = 61)	RC	EORTC QLQ-30 (POD3): 2 categories significantly better (physical and emotional function) EORTC QLQ-30 (POD7): 6 categories significantly better (role, emotional, cognitive, social functioning, fatigue, constipation) EORTC QLQ-30 (once home): 9 categories significantly better (physical, role, emotional, cognitive, social functioning, fatigue, dyspnea, insomnia, constipation)	Wound healing problem: 15% vs 38% ($P = .006$) Fever: 26% vs 54% ($P = .004$) DVT (0% vs 8%, $P = .027$), mobilization (nonsignificant) Narcotic usage ($P < .001$), PONV/POI (nonsignificant)
Maffezzini et al ⁶²	2012	68	Prospective	ERP	RC with Indiana pouch	Major surgical complications: 7 (10.3%) Major medical complications: 2 (3%)	Minor surgical complications: 4 (5.8%) Minor medical complications: 11 (16.2%)
Pruthi et al [¶]	2010	100	Retrospective	ERP	RC	Metoclopramide with and without: LOS, POI, GI complications (all nonsig), PONV (3% vs 12%, $P = .011$) Gum Chewing vs control: time to flatus (2.9 vs 2.4 days, $P < .001$); Time to BM (3.9 vs 3.2 days, $P < .001$); LOS (nonsig)	Mean time to flatus (2.2 days) Mean time to BM (2.9 days) Mean time to discharge (5.0 days) Complication rate (39% overall, 16% GI) Readmission rate (12%) Not reported
Arumainayagam et al ^{**63}	2008	112	Retrospective	Classic cohort (n = 56) ERP (n = 56)	RC	Median LOS (17 vs 13 days) ($P < .001$) Complications (major and minor): 41% vs 32% (nonsignificant) Readmissions 9% vs 5% (nonsignificant) Mortality 2% vs 2% (nonsignificant)	

BM, bowel movement; DVT, deep vein thrombosis; EORTC QLQ-30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; ERP, enhanced recovery protocol; LOS, length of stay; PONV, postoperative nausea and vomiting.

* All RC with variety of urinary diversion types except otherwise noted.

† A subgroup analysis was included, which featured expanded outcomes metrics and evolution of ERP.

‡ Comparative matched control data only provided for LOS.

§ Hospital stay is covered in Germany until removal of all catheters and drains.

¶ Only comparative data given for primary outcomes; secondary outcome was most recent ERP 100 patients.

** No P values provided for nonsignificant comparisons.

No differences were found in regard to pain scores, either in the immediate postoperative period or in surgical wards. Furthermore, total fentanyl requirement and satisfaction scores were similar for both groups.⁵⁷

There are no existing prospective studies comparing postoperative pain options after RC. A retrospective review of 308 patients found improved pain scores on postoperative day (POD)1 (3.2 vs 4.4, $P < .001$) and POD2 (2.53 vs 2.99, $P = .004$) and lower narcotic usage (45 mg vs 85 mg, $P < .001$) with EA vs PCA but no differences in LOS (9.7 vs 9.6 days, $P = .2$), POI (3.4% adjusted difference, $P = .6$), or overall complications (2.7% adjusted difference, $P = .7$) after multivariate analysis.⁵⁸ However, rectus sheath catheters with levobupivacaine bolus infusions (20 mL of 0.25% every 6 hours) have been described in RC and appear to contribute to a decreased LOS (17-10.8 days) as part of a multimodal anesthesia plan.⁵⁹

Adjuncts to epidural or regional anesthesia have also been described and may contribute to decreased narcotic use. Multimodal anesthesia with ketorolac reduces opiate usage and improves pain scores.⁶⁰ A recent meta-analysis, which included major abdominal surgeries and urologic patients, showed no increased risk of perioperative bleeding in patients receiving ketorolac with improved rates of postoperative nausea and vomiting.⁶⁴ A prior postmarketing study of parenteral ketorolac also showed no increased risk of operative site bleeding overall (odds ratio [OR] 1.02; 95% CI 0.95-1.10) or in a subgroup of patients older than 75 years of age (OR 1.12; 95% CI 0.94-1.35).⁶⁵

NGTs. Continuing prophylactic NGT placed intraoperatively during cystectomy was traditionally thought to prevent buildup of gas and fluids until the return of bowel function. Several studies in urology and a Cochrane review of nonurology abdominal surgeries have shown that early removal of NGT is actually beneficial—with earlier return of bowel function, fewer pulmonary complications, and no difference in bowel complications.⁶⁶⁻⁶⁸ NGT placement may actually increase the risk of aspiration pneumonia by making the esophageal-gastric sphincter incompetent.⁶⁹

Early Feeding and Ambulation. Early feeding is inherent to any ERP because postoperative starvation perpetuates the process of insulin resistance and protein catabolism. Early feeding can reduce this resistance⁷⁰ and does not increase morbidity or anastomotic complications in elective colorectal surgery. A Cochrane review of patients undergoing colorectal surgery receiving early feeding found no change in the rate of wound infection (RR 0.77, 95% CI 0.48-1.22), intra-abdominal abscess (RR 0.87, 95% CI 0.31-2.42), or anastomotic leaks or dehiscence (RR 0.69, 95% CI 0.36-1.32). LOS was not significantly different in the 2 groups ($P = .06$), but there was a higher relative risk of vomiting in the early feeding group (RR 1.27, 95% CI 1.01-1.61).⁷¹ One systematic review also concluded improved patient satisfaction with early feeding.⁷²

Though early enteral feeding has not been studied prospectively in RC, the effects of early postoperative total

parenteral nutrition (TPN) have been studied prospectively in 157 patients, with TPN starting on POD1 and continuing for 5 days. When comparing the TPN group with the standard nutrition group, we found a significantly higher rate of postoperative complications (69% vs 49%, $P = .013$), infectious complications (32% vs 11%, $P = .001$), and no effect on return of GI function or LOS (16 days vs 15.5 days, $P = .365$). When performing subgroup analysis on patients who were designated as malnourished preoperatively, we found no differences in overall (82% vs 52%, $P = .096$) or infectious (18% vs 13%, $P = .692$) complications between TPN and no TPN.⁷³

There are no studies establishing an independent association between improved outcomes and early ambulation. However, bed rest and sedentary activity following surgery has been associated with an increased risk of pulmonary and thromboembolic complications and contributes to muscle weakness and insulin resistance postoperatively.⁷⁴ All Enhanced Recovery After Surgery plans recommend inclusion of frequent and early ambulation, but an “aggressive structured mobility plan” results in significantly greater time out of bed (average of 105 [range 34-225] vs 8 [range 0-38] minutes, $P = .047$) than conventional care.⁷⁵

POI and Gum Chewing. The proposed mechanisms behind POI after RC likely include bowel manipulation, electrolyte shift, and narcotic administration.⁷⁶ POI is a significant contributor to extended LOS,⁷⁷ and an earlier return of bowel function may significantly improve time to discharge. Gum chewing affects the neurohormonal modulation of the gut via multiple hormonal and neural (vagal) afferent pathways that potentially counteract the sympathetic inhibition of motility and lead to faster return of bowel function.⁷⁸ Specific to RC, Kouba et al first demonstrated in a group of 102 RC patients that gum chewing beginning on POD1 would be associated with decreased time to first flatus (2.4 vs 2.9 days, $P < .001$) and time to BM (3.2 vs 3.9 days, $P < .001$).⁷⁹ Gum chewing proved to be effective in improving GI outcomes in patients who underwent robotic-assisted laparoscopic radical cystectomy as well. Choi et al demonstrated that in both open radical cystectomy and robotic-assisted laparoscopic radical cystectomy groups, there was a significant decrease in time to flatus and time to BM in the gum-chewing group.⁸⁰

Promotility Agents. A complete Cochrane review of systemic promotility agents details many of the traditional agents used in abdominal surgeries for POI.⁸¹ Alvimopan, a novel peripherally selective mu-opioid receptor antagonist, was recently approved by the Food and Drug Administration for use in RC. Efficacy was established in 5 of the 6 phase III clinical trials published to date, a summary of which can be found in Table 3.⁸²⁻⁸⁶ Specific to patients undergoing RC, a randomized multicenter double-blind placebo-controlled trial of 277 patients showed shorter mean time to GI-2 recovery, defined as toleration of solid food

Table 3. Alvimopan

Author	Year	Total Patients (n)	Study Design	Cohorts	Surgery	GI Recovery	Discharge Order Written
Buchler et al	2008	911	R, DB, M, PC	Alvimopan 6 mg vs placebo	Open abdominal surgery	GI-2: -14.3 hours, $P < .001$	Difference: -8.1 hours, $P = .47$
			R, DB, M, PC	Alvimopan 12 mg vs placebo	Open abdominal surgery	GI-2: -10.7 hours, $P = .008$	Difference: -5.9 hours, $P = .84$
Ludwig et al	2008	654	R, DB, M, PC	Alvimopan 12 mg vs placebo	Laparotomy with bowel resection	GI-2: HR 1.5, $P < .001$	HR 1.4, $P < .001$
Viscusi et al	2006	666	R, DB, PC	Alvimopan 6 mg vs placebo	Open laparotomy (BR or Hyst)	GI-2: HR 1.37, $P = .008$	HR 1.31, $P = .008$
			R, DB, PC	Alvimopan 12 mg vs placebo	Open laparotomy (BR or Hyst)	GI-2: HR 1.33, $P = .018$	HR 1.28, $P = .015$
Delaney et al	2005	451	R, DB, M, PC	Alvimopan 6 mg vs placebo	Open laparotomy (BR or Hyst)	GI-3: HR 1.45, $P = .003$	HR 1.5, $P < .001$
			R, DB, M, PC	Alvimopan 12 mg vs placebo	Open laparotomy (BR or Hyst)	GI-3: HR 1.28, $P = .059$	HR 1.18, $P = .17$
Wolff et al	2004	510	R, DB, M, PC	Alvimopan 6 mg vs placebo	Open laparotomy (BR or Hyst)	GI-2: HR 1.38, $P = .013$	HR 1.25, $P = .07$
			R, DB, M, PC	Alvimopan 12 mg vs placebo	Open laparotomy (BR or Hyst)	GI-2: HR 1.67, $P < .001$	HR 1.42, $P = .003$
Lee et al	2014	280	R, DB, M, PC	Alvimopan 12 mg vs placebo	Radical cystectomy with urinary diversion	GI-2: HR 1.77, $P < .0001$	HR 1.69, $P < .001$

BR, bowel resection; DB, double blinded; DOW, discharge order written; GI-2, toleration of solid food and BM; GI-3, toleration of solid food and BM or flatus; Hyst, hysterectomy; M, multicentered; PC, placebo controlled; R, randomized.

and first BM (5.5 vs 6.8 days, HR 1.77; 95% CI 1.4-2.3; $P < .0001$), and shorter mean time to discharge order written (6.9 vs 7.8 days; HR: 1.67; 95% CI 1.3-2.2; $P < .001$). There was no significant difference in the rates of readmission between the 2 groups.⁸⁷ A subsequent economic analysis demonstrated an additional \$800 per patient cost of alvimopan and lower POI-related hospital costs (\$14,677 vs \$17,720, $P = .007$) but no significant difference in total hospitalization (\$18,087 vs 20,726, $P = .148$).⁸⁸

Extended Venous Thromboembolism (VTE)

Prophylaxis. Rates of deep vein thrombosis and pulmonary embolism in the perioperative period of RC range from 0.6% to 4.7% and from 0.6% to 2.0%, respectively.⁸⁹⁻⁹² Although the risk factors for VTE are common to the patient with bladder cancer, it has also been established that surgery itself is an independent risk factor for developing VTE.⁸⁹ Development of VTE has been linked to increased 30-day⁹¹ and 2-year mortality.⁸⁹ The timing of developing VTE is an important consideration as 2 studies demonstrated that the majority of VTEs developed after patients were discharged to home at an average of postoperative day 15.^{90,91} Although patients should receive both mechanical and chemical prophylaxis during hospitalization,⁹³ only recently has there been recognition of the need for extended outpatient chemoprophylaxis for RC patients. Both of these studies confirm the potential benefit of extended 4-week prophylaxis in high-risk patients.⁹³ Low-molecular-weight heparins have similar efficacy to coumadin in the prevention of cancer-related VTE with a superior side effect profile, though this has not been tested in postsurgical patients.⁹⁴ However, there are safety concerns in using extended VTE prophylaxis, specifically post RC, based on perioperative fluctuations in renal function that may lead to supratherapeutic levels of low-molecular-weight heparins. Patients with preoperative poorer renal function (estimated glomerular filtration rate <60 mL/min/1.73 m²) may be at an even greater risk (OR 9.1, 95% CI 4.3-19.3; $P < .001$).⁹⁵ Dalteparin is thought to have a possible anti-neoplastic effect as well.⁹⁶ To date, no randomized studies have demonstrated a survival benefit for extended anticoagulation after cystectomy.

CONCLUSION

Care redesign is an ambitious but necessary undertaking in RC as the medical landscape is changing. We have reviewed the data involving perioperative management of the RC patient with a focus on improving many traditional outcome measures and factors. These interventions can be implemented regardless of the operative approach—robotic or open. Urologists will need to adopt care redesign as a habit rather than a single intervention and must continue to work as a healthcare team to evolve to improve care and intelligently combat rising healthcare costs. We hope that this review will help guide further improvements of RC care.

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APPENDIX

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.urology.2015.09.001.