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Updates on enhanced recovery after surgery for radical cystectomy

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***Abstract*:** Enhanced Recovery after Surgery (ERAS) is a multimodal pathway that provides evidence-based guidance for improving perioperative care and outcomes in patients undergoing surgery. In 2013, the ERAS society released its original guidelines for radical cystectomy (RC) for bladder cancer (BC), adopting much of its supporting data from colorectal literature. In the last decade, growing interest in ERAS has increased RC-specific ERAS research, including prospective randomized controlled trials (RCTs). Collective data suggest ERAS contributes to improved complication rates, decreased hospital length-of-stay, and/or time to bowel recovery. Various institutions have adopted modified versions of the ERAS pathway, yet there remains a lack of consensus on the efficacy of specific ERAS items and standardization of the protocol. In this review, we summarize updated evidence and practice patterns of ERAS pathways for RC since the introduction of the original 2013 guidelines. Novel target interventions, including use of immunonutrition, prehabilitation, alvimopan, and methods of local analgesia are reviewed. Finally, we discuss barriers to implementing and future steps in advancing the ERAS movement.

Keywords: bladder cancer, cystectomy, enhanced recovery, ERAS

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Introduction

In 2022, an estimated 81,000 new cases of bladder cancer (BC) will be diagnosed with over 17,000 deaths in the United States.[1] Radical cystectomy (RC) is the gold standard for managing patients with muscle-invasive BC (MIBC) and non-muscle invasive BC (NMIBC) at high risk of recurrence and progression.[2] While potentially curative, RC is associated with high risk of morbidity and mortality. In contemporary data, 30-day readmission rates remain high at 25% and 90-day complication rates approach 65%.[3–5] Nearly 40% of patients are diagnosed at ⩾75 years of age and > 60% have at least one serious comorbidity, both of which are factors associated with worsened outcomes.[6]

The multimodal enhanced recovery after surgery (ERAS) pathways for RC, first adopted from colorectal literature, were designed to provide evidence-based guidance for improving perioperative care and outcomes.[7] The initial guidelines released by the ERAS society in 2013 outlined 22 targetable items, of which only seven items had sufficient evidence. These included oral mechanical bowel preparation, minimally invasive approach, perioperative fluid management, nasogastric intubation, urinary drainage, prevention of postoperative ileus, and prevention of postoperative nausea/vomiting. In the colorectal field, meta-analyses demonstrated high level evidence for reduced complication rates and postoperative hospital length-of-stay (LOS) associated with ERAS pathways. Nevertheless, adoption of ERAS in the urologic community was slow and many criticized the lack of prospective randomized controlled trials (RCT) evidence in this space.

In the past decade, various institutions have adopted modified versions of the ERAS protocol that was introduced in 2013.[8] Since then, increased interest in the ERAS pathway has resulted in studies that provide cystectomy-specific evidence for the use of ERAS on optimizing perioperative care.[8,9] In 2018, the American

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Urological Association (AUA) published comprehensive guidelines for optimizing postoperative outcomes in urologic surgery, which was based off the ERAS movement.[10] Nevertheless, ERAS remains a growing movement for which standardization has not yet been achieved. The purpose of this review is to provide updated evidence on outcomes and describe contemporary practice patterns for ERAS in patients undergoing RC for BC. Looking forward, we discuss limitations and future steps in advancing the movement.

Comprehensive ERAS protocols

When the ERAS guidelines for RC were published in 2013, much of the evidence originated from colorectal literature. Early observational studies demonstrated inconsistent findings across outcomes of interest including hospital LOS, time to bowel recovery, and rates of readmission.[9] Since this time, rising enthusiasm for ERAS has resulted in increased publication of RC-specific trials. In 2020, Williams *et al.* conducted a systematic review of 22 international studies, including four RCTs. In addition to the core ERAS components reviewed by Tyson *et al.* in 2016, the authors looked at interventions such as prehabilitation and use of local versus epidural anesthesia, for which data had become available. Results demonstrated reduced morbidity, time to bowel recovery, and LOS in ERAS patients without significant difference in mortality.[9] Specific ERAS items contributing to shorter LOS included no NGT (regression coefficient -8.70 days, 95% CI: -11.9 to -5.53, $p < 0.001$) and use of local compared to epidural anesthesia (regression coefficient -3.29 days, 95% CI: -6.31 to -0.27, $p = 0.03$).

Several prospective RCTs have contributed to the growing evidence pool for ERAS following RC and warrant individual discussion.[11–14] In 2018, Lin *et al.*[15] conducted a RCT from 2014 to 2016 among 25 centers of the Chinese BC Consortium to determine the efficacy of ERAS for RC. One hundred forty four patients were randomized to the ERAS arm and 145 to the conventional arm. Targeted items in the ERAS cohort consisted of preoperative education, no postoperative NGT, clear fluids 2 h after surgery, early ambulation, and administration of prokinetic agents. The ERAS cohort experienced a reduced rate of postoperative complications (25.7 vs 30.3%, $p = 0.40$) without differences in severity or types of complications. ERAS patients also had reduced median time to first bowel movement (88vs 100 h, $p = 0.01$), liquid diet (68 vs 96 h, $p < 0.001$), regular diet (125 vs 168 h, $p = 0.004$) and ambulation (64 vs 72 h, $p = 0.047$). Hospital LOS was not affected, which may be attributable to the design of the international healthcare system studied. It is important to consider limitations in generalizing these study findings to populations in the United States, where ambulation and transition to regular diet are encouraged on postoperative day (POD) 0-1 and early discharge is incentivized. In the same year, Frees *et al.*[16] published a prospective pilot RCT comparing prospective outcomes with ERAS versus conventional care in a Canadian cohort. ERAS distinctive interventions included preoperative nutrition, goal-directed fluid therapy (GDFT), promotility agent use, postoperative gum chewing, and early transition to liquid diet. The cohort was small, consisting of 12 ERAS patients and 15 standard care patients. Findings showed that the ERAS cohort had significantly shorter mean hospital LOS (6.1 vs 7.39 days, $p = 0.020$), time to first flatulence (2.5 vs 3.62 days, $p = 0.011$), and time to first bowel movement (4.3 vs 6.31 days, $p = 0.009$). ERAS patients also subjectively reported reduced postoperative pain and quality of life related to bowel symptoms at time of discharge. More recently in 2020, Vlad *et al.*[17] published a prospective RCT of 90 consecutive BC patients undergoing RC at a Romanian institution. Their ERAS protocol was adapted from the 2013 ERAS guidelines and included interventions such as preoperative counseling and education, omitting bowel preparation, intraoperative fluid restriction, early mobilization, and measures to prevent ileus. Patients following the ERAS protocol were found to have significantly lower time to flatus (1 vs 5 days, $p < 0.001$), bowel movement (2 vs 5 days, $p < 0.001$), regular diet (5 vs 6 days, $p < 0.001$), and discharge (16 vs. 18 days, $p < 0.001$).[18] Consistent with most European countries, the authors emphasized the structure of their healthcare system in which use of outpatient care is limited and patients are typically discharged only after all drains and catheters are removed.

Collective data demonstrates improved complication rates, bowel recovery, and LOS using ERAS pathways, which can be adopted across diverse healthcare systems and institutions.[8] Contemporary studies have incorporated novel evidence-based interventions including prehabilitation and the preferred use of regional anesthesia. The ERAS

Table 1. Example of updated ERAS protocol compared to 2013 ERAS guidelines for RC.

2013 ERAS Guideline Protocol[7]	Example of Updated ERAS Protocol[12]
Preoperative	*Preoperative*
Preoperative counseling and education	Preoperative counseling and education
Preoperative medical optimization	Prehabilitation exercise (walking for 1 h/day)
Correction of anemia and comorbidities	Preoperative medical optimization
Nutritional support	Optimization of comorbidities
Smoking cessation/reduction of alcohol	Smoking cessation advice
Encourage physical exercise	Correction of anemia
Oral mechanical bowel preparation omitted	Oral mechanical bowel preparation omitted
Thrombosis prophylaxis with compression	**Self-administered thromboprophylaxis**
stockings and LMWH	**12 h prior to surgery, at home**
Preoperative carbohydrate loading	Preoperative carbohydrate loading
Preoperative oral intake	Preoperative oral intake
Pre-anesthesia medication	Pre-anesthesia medication
Intraoperative	*Intraoperative*
Standard anesthetic protocol	Standard anesthetic protocol
Antimicrobial prophylaxis	Antimicrobial prophylaxis
Skin preparation	Skin preparation
Thromboembolic prophylaxis	Thromboembolic prophylaxis
Epidural anesthesia	**Regional anesthesia**
Perioperative fluid management	**Epidural anesthesia omitted**
Nasogastric intubation omitted	**Rectus sheath catheters (0.125% bupivacaine) for 48h**
Preventing intraoperative hypothermia	Perioperative fluid management
Minimally invasive approach	Nasogastric intubation omitted
Resection site drainage	Preventing intraoperative hypothermia
Urinary drainage	Minimally invasive approach
Postoperative	Resection site drainage
Postoperative diet	Urinary drainage
Early oral diet	**Wound closure**
Prevention of postoperative ileus	**2/0 polydioxanone suture to rectus sheath**
Prevention of PONV	**3/0 subcuticular Monocryl suture to skin**
Postoperative analgesia	*Postoperative*
Including epidural anesthesia	Postoperative diet
Early mobilization	Early oral diet
Audit	Prevention of postoperative ileus
	Prevention of PONV
	Postoperative analgesia
	Including rectus sheath catheters (0.125% bupivacaine)
	Early mobilization
	Audit

Updates bolded.

movement is dynamically growing; guidelines on previously described items are refined as availability of data and newer interventions continue to be actively investigated (Table 1).

Targeted components of ERAS

Preoperative counseling and setting expectations

Preoperative education for patients undergoing RC includes counseling and managing patient expectations on surgical details, hospital stay and discharge criteria, stoma use, and postoperative complications.[7] Preoperative preparation and patient expectation have been shown to impact patient satisfaction across various surgical fields.[19–21] Implementation of cystectomy education can vary according to the resources available at an institution and range from structured educational classes to oral and written information provided at the time to preoperative counseling.[14,22] Data on optimal methods of preoperative education were limited in the 2013 ERAS guidelines and unsurprisingly, this continues to remain the case.

Specific components of preoperative education have been explored in early studies. Jensen *et al.*[23] conducted a prospective RCT of 107 patients investigating the efficacy of a preoperative stoma education program on an individual's ability to independently change a stoma-appliance. Patients randomized to the intervention were provided home-based training kits and expectation counseling for post-cystectomy life, while the standard group did not receive any education. The intervention group had significantly higher Urostomy Education Scale scores (Standardized mean difference 2.7, 4.3, and 5.1 at 35, 120, and 365 days postoperatively, respectively), which have been validated to demonstrate urostomy self-care skills. Sexual recovery is another aspect of post-cystectomy care that significantly impacts patient quality of life. Loh-Doyle *et al.*[24] reported a Median International Index of Erectile Function (IIEF-5) score of 1 (IQR:1–11) in 134 post-RC patients, compared to 16 (IQR:5–23) preoperatively. In a qualitative study, Westermen *et al.*[25] similarly found that found that many women experienced sexual dysfunction following RC (12/22, 54.5%) and desired more preoperative counseling. Based on this feedback, the authors have incorporated material regarding sexual function into their standardized preoperative education. Efficacy of this intervention on patient outcomes and satisfaction remain to be studied.

There is no current standardized model for effective, evidence-based preoperative education. Aiming to identify opportunities for improving care delivery, Smith *et al.*[26] conducted a qualitative study to elucidate the perioperative experiences of providers, patients, and caretakers at their institution. Cystectomy education consisted of counseling and formal written materials at two timepoints, once during the preoperative visit and once during the postoperative discharge process. Upon interview, all parties acknowledged the issue of information overload and the need for incremental learning across multiple encounters to process the overwhelming material. One patient succinctly described the experience as "drinking water out of a fire hydrant." Notably, patients diverged on their preferred source of information. Some patients found it most helpful to speak with acquaintances who had undergone the same surgery while others preferred to learning from their medical providers. Both preferences were based on level of trust. The authors recognized a need for improved understanding of postoperative expectations, including both normal and abnormal symptoms. More importantly, patients needed "the right information at the right time," which patients defined as "the time at which postoperative symptoms are experienced." The authors proposed a conceptual model of a mobile health intervention that facilitates incremental learning, tracks patient-reported outcomes, and provides two-way communication between the provider and patient. Metcalf *et al.* conducted a pilot trial in 20 patients assessing the feasibility of an iPad-based healthcare application which released pertinent educational videos at specific time points prior to surgery. In addition, iPad-syncing devices to measure perioperative ambulation and vital signs were provided that produced automated triggers to inform the study team of significant abnormalities. Current barriers to preoperative education include travel distance to healthcare facility and level of health literacy. In an era where technology is being increasingly utilized by the older population, it will be exciting to assess the efficacy of personalized mobile interventions to improve patient care and outcomes.[27] While it is challenging to measure the efficacy of specific educational approaches, it is clear there remains room for significant improvement. Preoperative counseling is a vital component of ERAS that must continue to be studied and optimized.

Preoperative optimization

Risk stratification. The 2013 ERAS guidelines cited the association of preoperative nutritional status with postoperative mortality rates and recommended preoperative oral nutritional support, especially in malnourished patients.[7,28] Since then, significant strides have been made in identifying comprehensive patient-related factors that require optimization prior to undergoing a major operation such as RC. BC is described as a catabolic disease process and undergoing RC leads to an increased resting energy expenditure.[29] Malnutrition, estimated in 16%−33% of RC populations, is a strong predictor of 90-day mortality and overall survival.[28,29] Closely related to malnutrition, frailty is a "decrease in physiologic reserve distinct from disability or comorbidity," and has been repeatedly associated with increased morbidity and mortality in patients undergoing RC for BC.[30–33] RC patients are often at increased susceptibility of nutritional deficiency and frailty with older age, cancer-associated cachexia, and receipt of neoadjuvant chemotherapy.[34] Palumbo *et al.*[35] demonstrated that frailty was the most consistent and strongest predictor of early adverse outcomes after RC, over advanced age and comorbidities. More recently, sarcopenia, defined as degenerative loss of muscle mass, has garnered interest as an objectively measurable component of frailty and poor prognostic factor for this population.[36–38] Skeletal muscle index, the total lumbar muscle area at mid-L3 divided by height^2 (cm^2/m^2) on axial computed tomography scans is the most strongly validated index for sarcopenia.[39] Michel *et al.*[40] outlined screening tools used to identify patients at risk for malnutrition, including Nutritional Risk Screening (NRS-2002) and Malnutrition Universal Screening Tool, which are the most strongly validated in oncologic populations. The Patient-Generated Subjective Global Assessment (PG-SGA), which incorporates physical assessment is also highlighted as an effective option for screening. Identification of such modifiable risk factors have led to advancements in early preoperative interventions, namely, "immunonutrition" and "prehabilitation."

Immunonutrition. Limited studies have found potential benefits in providing various perioperative nutrition interventions for RC. A Cochrane review by Burden *et al.*[41] has further corroborated that across various perioperative nutrition interventions there is a paucity of evidence for improving perioperative outcomes.[42] Specifically, the goal of "immunonutrition" is to provide nutritional support that augments the patient's immune system.[43] Arginine has been studied in colorectal oncologic literature as an immunonutrient that significantly decreases the rate of postoperative infections and hospital LOS.[44] In the first prospective RCT in RC patients conducted by Hamilton-Reeves *et al.*[45] on this topic, 14 men were randomized to receive specialized immunonutrition while 15 received an oral nutritional supplement (ONS). Both groups drank three cartons daily for 5 days prior to and following RC. Myeloid-derived suppressor cell count was significantly lower in the immunonutrition group after RC ($p < 0.001$), signifying an improved immune responsive against infection. Neutrophil: lymphocyte ratio was also significantly reduced after the first incision ($p = 0.039$). Clinically, patients receiving immunonutrition had a 33% reduced postoperative complication rate (95% CI: 1–64, $p = 0.060$) and a 39% reduced infection rate (95% CI: 8–70, $p = 0.027$), findings supported by similar retrospective trials.[46,47] In a follow-up study, the authors analyzed the same cohort to asses effects on short-term inflammatory response and arginine status.[48] In the immunonutrition cohort, authors found a 54.3% increase in the Th1-Th2 balance, which signifies reduced infectious risk; a 4.8% decrease was noted in the ONS group ($p < 0.027$). In addition, plasma interleukin-6 (IL-6) was 42.8% lower in the immunonutrition group compared to the ONS group ($p = 0.020$), which reflects level of muscle wasting. Plasma arginine levels were maintained in the immunonutrition group from baseline to POD 2, while a 26.3% reduction of levels was seen in the nutritional supplement group ($p = 0.0003$). Currently, these preliminary findings for improved clinical outcomes associated with immunonutrition are being validated in a multi-center phase-III RCT, SWOG 1600 or SIMmune (NCT03757949), with an expected completion date of December 2023.[49]

Prehabilitation. Similarly, the goal of "prehabilitation" is to improve functional status prior to the beginning of acute treatment to better endure the physical challenges of a major surgery such as RC.[50] Prehabilitation itself is a multimodal intervention that can require the multidisciplinary support of nutritionists, physical therapists, and urologic oncology nurses, in addition to the primary medical team. While there is currently a lack of consensus and evidence for a standardized prehabilitation program, exercise and nutrition are commonly included components. In 2014, Jensen *et al.*[51] conducted an early prospective RTC in which 50 RC patients were randomized to the intervention arm and 50 to the standard arm. Prehabilitation interventions included 2 weeks of preoperative strength and endurance exercises in addition to progressive postoperative mobilization. About 60% of patients adhered to at least 75% of the primarily home-based program. Postoperative mobilization, measured by walking distance and ability to perform personal activities of daily living, were significantly improved in the intervention group ($p \leqslant 0.001$ and $p \leqslant 0.05$, respectively). No significant differences were reported in LOS or severity of complications. More recently, a phase I/II study by Kaye *et al.*[52] aimed to assess the feasibility and safety of a prehabilitation program for RC patients. The trial enrolled 54 patients $\geqslant 60$ years old, with a Karnofsky performance score $\geqslant 70$ and a sedentary baseline lifestyle undergoing RC into a four-week supervised preoperative exercise training program. Successful compliance, defined as adherence to $> 70\%$ of sessions was achieved by 80.4% of patients. Postoperatively, distance walked improved by 58.5 feet ($p < 0.001$) and patients reported improved quality of life post-exercise ($p < 0.015$), with mental components sustained 90-days postoperatively ($p < 0.015$). Minnella *et al.*[53] reported supportive findings in a prospective, institutional RCT that randomized 35 RC patients to multimodal prehabilitation and 35 to standard care. The intervention consisted of preoperative aerobic and resistance exercises, diet therapy, and relaxation techniques. Initially, no significant difference in functional capacity was noted between the two groups. However, four weeks postoperatively, the prehabilitation group had significantly higher functional capacity as measured by a 6-min walk test. (142.5 vs 126 m, $p = 0.014$). While these findings reached statistical significance, the clinical significance on outcomes remains unclear. Looking specifically at the effects of an enriched oral nutrition, Ritch *et al.*[54] conducted a prospective RCT and found that 31 patients randomized to ONS had reduced weight loss (-5 vs -6.5 kg, $p = 0.04$) compared to 30 patients in the standard multivitamin group. In addition, the prevalence in sarcopenia remained stable with ONS while a 20% increase was noted in the multivitamin group ($p = 0.01$).

The role of prehabilitation in the ERAS pathway and its long-term benefits in reducing postoperative morbidity are not well understood. Larger, multi-centered RCTs such as PREPARE-ABC and Prehab4cancer are being conducted in the colorectal and surgical oncology fields.[55,56] Much work remains to be done in refining a program that is not only beneficial but adherable for BC patients and implementable by clinical team members. Prehabilitation programs are resource-intensive and can require upfront financial investments, which can be prohibitive in certain circumstances. In one qualitative study, health professionals described the challenges of identifying suitable patients through pre-screening and providing one-on-one time for interventions within existing workflows.[57] In addition, interventions for mental and sexual health have yet to be well-studied in the context of prehabilitation and await investigation.[58]

Smoking cessation. Surgical literature has consistently reported increased postoperative complications associated with smoking, which can be reduced with cessation 4–8 weeks before surgery.[59,60] Similarly, a systematic review based primarily on retrospective studies between 2000 and 2020 found increased morbidity and mortality with smoking in patients undergoing RC for BC.[61] Recently, Vahr Lauridsen *et al.* published results from the prospective randomized STOP-OP trial, evaluating the efficacy of smoking and/or alcohol cessation interventions in ERAS patients undergoing RC. No significant difference was found in 30-day complication rates between 52 control group patients and 52 patients highly compliant to a 6-week intensive cessation intervention (70 vs 64%, RR: 0.91, 95% CI: 0.68–1.21, $p = 0.51$). Twenty seven percent of patients in the control group and 51% in the intervention group successfully quit smoking (RR: 2, 95% CI: 1.14–3.51, $p = 0.01$). Importantly, the median time from quitting to surgery was 2 days, which may explain the discrepancy with literature. Future studies are needed to evaluate the impact of cessation interventions 4–8 weeks in advance of surgery.

GI recovery—Alvimopan

Gastrointestinal (GI) complications are experienced in up to 30% of patients in the early postoperative period.[62] Postoperative ileus (POI) is among the most common GI complications and is associated with prolonged hospital LOS, increased morbidity, and increased costs.[63] Multiple items in the 2013 ERAS guidelines such as early removal of nasogastric tube (NGT), gum chewing, oral magnesium, anti-emetic prophylaxis, and early oral diet are aimed to reduce GI-related complications.[7,64] Multiple studies have supported the claim of improved GI outcomes, measured by return of bowel function, with implementation of ERAS protocols.[16,65,66] Using prospectively collected data, Bazargani *et al.*[67] conducted a study looking specifically at GI complications following RC in patients treated with ERAS. Independent of other variables, 292 ERAS patients had significantly reduced GI complications compared to 144 patients in the control group (13 vs 27%, $p = 0.003$) at 30 days. Rate of POI was 7% in the ERAS group compared to 23% in the control group ($p < 0.001$). There was no significant difference in 30-day readmission rates (10 vs 5%, $p = 0.1$). Of note, this specific institutional ERAS protocol included the use of alvimopan to accelerate return of bowel function.

Alvimopan is an oral, peripheral antagonist of the μ-opioid receptor that enhances GI recovery.[68] In 2013, the Federal Drug Administration approved alvimopan for the indication of accelerating time to upper and lower GI recovery following surgeries that include partial bowel resection with primary anastomosis. Multiple phase III RCTs have reported reduced time to return of bowel function, postoperative complications, hospital LOS, and rate of readmission following bowel resection and total abdominal hysterectomy in patients who received alvimopan compared to placebo groups.[68–71] Retrospective studies using institutional as well as nationwide databases demonstrate reduced LOS and time to GI recovery with alvimopan use in RC patients.[72–74] Although alvimopan was not initially included in the 2013 ERAS guidelines, it has been increasingly adapted into protocols following a RC-specific multicenter RCT published by Lee *et al.*[75] This study found that patients randomized to alvimopan ($n = 143$) had reduced time to GI recovery (5.5 vs 6.8 days, HR 1.8, $p < 0.0001$), mean LOS (7.4 vs 10.1 days, $p = 0.0051$), NGT insertion (7.7 vs 24.6%, $p < 0.001$), and episodes of POI-related morbidity (8.4 vs 29.1%, $p < 0.001$) than patients randomized to placebo ($n = 137$). Incidence of all other adverse events and 30-day readmission rates (23.8 vs 26.9%, $p = 0.58$) were not significantly affected. Correspondingly, the AUA guidelines for treatment of non-metastatic MIBC now strongly recommend the use of μ-opioid antagonists to accelerate GI recovery in patients undergoing RC.[76]

Intraoperative fluid management and transfusion

Fluid restriction. In the past, fluid restriction was promoted in patients undergoing surgery to achieve a zero balance and reduce complications associated with postoperative fluid overload.[77] In 2018, the largest international RCT investigating fluid management for major abdominal surgery was published. Authors of the RELIEF trial compared survival outcomes and complication rates between 1,490 patients who received restrictive fluid therapy and 1,493 patients who received a liberal intravenous fluid regimen.[78] Of note, 14.8% and 14.9% of the respective cohorts underwent urologic or renal surgeries. The restrictive cohort received a median intravenous-fluid intake of 3.7 L compared to 6.1 L in the liberal cohort ($p < 0.001$).[78] Similar rates of disability-free survival were reported at 1 year for the restrictive (81.9%) and liberal (82.3%) cohorts (HR: 1.05, 95% CI: 0.88–1.24, $p = 0.61$). This effect remained consistent even after accounting for use of a goal-directed device ($p = 0.37$) and the employment of other ERAS principles in less than half of patients. However, the rate of acute kidney injury (AKI) was higher (8.6%) in the restrictive group compared to the liberal fluid group (5.0%) ($p < 0.001$). In a prospective observational study, Bazargani *et al.*[79] analyzed the association between intraoperative fluid intake and postoperative complications in 180 patients undergoing RC with ERAS protocol and reported similar findings. Intraoperative fluid restriction was not independently associated with significant changes in LOS ($p = 0.099$) and 30 ($p = 0.88$) or 90-day ($p = 0.62$) complications. In summary, non-individualized fluid restriction has failed to demonstrate significant differences in outcomes of surgical patients.

Goal-directed fluid therapy. Goal-directed fluid therapy (GDFT) in modern ERAS protocols aims to minimize complications associated with both fluid excess and hypovolemia. The fundamental principle is to optimize cardiac preload and tissue oxygen delivery using evidence-based hemodynamic parameters.[80] Commonly utilized techniques include transesophageal echocardiography, pulmonary artery catheterization, arterial waveform analysis-based techniques, and transesophageal Doppler.[81] These techniques measure key parameters including cardiac index, stroke volume variation (SVV), mixed venous oxygen saturation (SvO2), and systemic vascular resistance. The original 2013 ERAS society guidelines recommended targeting cardiac output using the esophageal Doppler system (or other similar systems) and using vasopressors judiciously for arterial hypotension.[7]

As with many components of ERAS, much of the evidence for GDFT stems from the colorectal field, where positive fluid balance has been associated with delayed return of bowel function and prolonged LOS.[82] Contemporary reviews have demonstrated mixed findings. In a 2014 meta-analysis looking at 961 patients undergoing 11 major abdominal, two cardiac, and one thoracic surgeries, Benes *et al.*[83] found that GDFT reduced postoperative morbidity (OR: 0.51, 95% CI: 0.34–0.74, $p < 0.001$). Decreased morbidity was related to a reduction in infectious (OR: 0.45, 95% CI: 0.27–0.74, $p = 0.002$), cardiovascular (OR: 0.55, 95% CI: 0.36–0.82, $p = 0.004$), and abdominal (OR: 0.56, CI: 0.37–0.86, $p = 0.008$) complications, as well as in length of intensive care unit (ICU) stay (weighted mean difference -0.75 days, 95% CI: -1.37 to -0.12, $p = 0.02$). In contrast, a meta-analysis of 2,910 patients in 37 studies, including one urological and 20 abdominal-based trials, Deng *et al.*[84] found that GDFT alone did not significantly reduce short-term mortality, overall morbidity, organ-specific morbidity, or hospital/ICU LOS. Interestingly, Rollins *et al.*[85] conducted a meta-analysis of 23 RCT's and found that while GDFT was associated with a significant reduction in morbidity (RR: 0.76, 95% CI: 0.66–0.89, $p=0.0007$), hospital LOS (mean difference -1.55 days, 95% CI: -1.18 to -0.09, $p=0.02$), and time to first bowel movement (mean difference -0.90 days, 95% CI: -1.48 to -0.32 days, $p=0.002$), no significant reductions were seen in overall morbidity and total hospital LOS when patients were managed on the ERAS pathway. In 2018, authors of the FEDORA trial published a prospective RCT comparing postoperative complications in 224 patients managed with goal-directed hemodynamic therapy (GDHT) compared to 226 managed with traditional principles.[86] In the GDHT group, esophageal Doppler cardiac output monitor measured SVV, cardiac index, and mean arterial pressure to guide use of fluids and vasopressor/inotropic drugs. The GDHT group had significantly reduced complications (8.6% vs 16.6%, $p=0.018$), time to ambulation (2 vs 3 days, $p<0.001$), hospital LOS (5 vs 6 days, $p=0.001$), and ICU LOS (16 vs 24 h, $p<0.001$). However, no significant difference in mortality was found at 180 days. The ERAS pathway was otherwise not employed in this trial.

RC presents unique challenges including prolonged operative time, increased risk of intraoperative bleeding, and unreliable urine output associated with clipping of the ureters.[87] Until recently, RC-specific evidence for use of GDFT had been limited to obvservational studies.[87] Arslan-Carlon *et al.*[88] at Memorial Sloan Kettering Cancer Center (MSKCC) conducted a prospective RCT comparing postoperative ileus in 142 patients managed with GDFT and 141 patients managed traditionally during open RC. In the GDFT cohort, the EV1000 clinical platform via a FloTrac™ sensor was utilized to measure hemodynamic parameters, primarily SVV. All patients were treated on the standardized postoperative ERAS pathway. No significant differences in postoperative ileus (difference in proportions 4.1%, 95% CI: -5.8% to 13.9%, $p=0.418$) or other high-grade complications (difference in proportions -2.2%, 95% CI: -10.6 to 6.1, $p = .602$) were found. However, increased rates of AKI were reported in the GDFT arm (56%) compared to the standard arm (40%) (difference in proportions 16.6%, 95% CI: 5.1–28.1, $p=0.005$; $p=0.170$ after adjustment for multiple testing). The authors concluded that GDFT may not be effective for reducing postoperative ileus in the setting of open RC.

AKI remains the primary concern for optimizing fluid balance through GDFT in patients undergoing RC. Akin to the findings of the prospective MSKCC trial, Hanna *et al.* analyzed a retrospective institutional cohort of 146 pre-ERAS and 150 ERAS patients who underwent RC between 2010 and 2018. An increased rate of postoperative AKI in patients on the ERAS pathway (42.7% vs 30.1%, $p=0.025$) was reported without impact on LOS or readmission rates. Evidence for the most effective intravenous fluid regimen and GDFT technique remains unclear. Further multi-centered, prospective trials are warranted to better understand optimal fluid management in patients undergoing RC and treated on the ERAS pathway. In addition, further analyses should be conducted to identify patients at increased risk for AKI in this population.

Perioperative blood transfusions. It is well-established that perioperative blood transfusions (PBT) and their immunosuppressive effects increase cancer recurrence and mortality for many solid organ tumors.[89,90] Although controversial, these oncologic outcomes have also been demonstrated for patients with BC undergoing RC.[91–93] The AUA currently recommends avoiding intraoperative blood transfusions, if possible.[94] However, the effects of transfusion on surgical outcomes related to the goals of ERAS are not well understood. Some institutions have incorporated a restrictive transfusion protocol into their standardized ERAS protocol, though this is not practiced universally.[10] Diamantopoulos *et al.*[95] retrospectively found that PBT did not increase the risk for postoperative complications, but was associated with prolonged hospitalization $\geqslant 10$ days in the setting of RC (aOR: 2.30, 95% CI: 1.13–4.7, $p=0.022$). Syan-Bhanvadia *et al.*[96] conducted a retrospective study investigating the safety of a restrictive transfusion protocol between 173 patients who were transfused restrictively and 87 matched patients transfused liberally. Compared to the liberal cohort, the restrictive group had reduced 90-day (65.6% vs 86.7%, $p=0.007$) and high-grade (15.6% vs 34.8%, $p=0.003$) complication rates. On multivariate analysis, PBT was associated with lower recurrence-free (HR: 2.16, 95% CI: 1.13–41.12,

$p=0.02$) and overall (HR 2.25, 95% CI: 1.25–4.88, $p=0.01$) survival. While early studies suggest reduced LOS and complication rates associated with restrictive transfusions, future, larger, prospective studies are required to support and improve ERAS guidelines surrounding PBT.

It is important to note that preoperative anemia has been associated with worsened outcomes in patients undergoing RC. Patients with MIBC often undergo neoadjuvant chemotherapy, which may be associated with bone marrow suppression. A systematic review of 17 studies by Xia and Guzzo[97] found that preoperative anemia and low hemoglobin were associated with increased all-cause mortality (HR: 1.75, 95% CI: 1.48 to 2.05, $p < .00001$), cancer-specific mortality (HR: 1.80, 95% CI: 1.45 to 2.25, $p < .00001$), and cancer recurrence (HR: 1.37, 95% CI: 1.16 to 1.62, $p = .0002$). Expectedly, preoperative anemia can be associated with increased PBT.[98,99] Thus, the effects of preoperative anemia on clinical outcomes have not been clearly delineated from those of PBT. Nevertheless, the correction of anemia, as highlighted in the 2013 ERAS guidelines, is an important component of medical optimization prior to surgery.[7]

Infection control

Infections are one of the most common sources of postoperative complications and readmissions after RC.[100] The 2013 ERAS guidelines recommend a single course of a second or third generation cephalosporin 1 h before skin incision, in addition to skin preparation with chlorhexidine-alcohol to prevent surgical site infection (SSI). Altobelli *et al.*[101] compared a cohort of pre- and post-ERAS RC patients and found that the incidence of readmissions remained comparable (30% pre-ERAS vs 27% post-ERAS). Up to 60% of readmissions had infectious causes, despite stringent adherence to the 2013 ERAS guidelines. The authors noted that about 60% of urinary tract infections (UTIs) were caused by *Entercoccus*, which was not well-covered by their current antibiotic choice. In a retrospective study, Haider *et al.*[102] also reported an incidence of 19.4% (42/217), of whom 50% developed urosepsis or uroseptic shock. In this cohort of three institutions, antibiotics were started with induction of anesthesia and continued according to institutional guidelines. The duration was not noted to impact risk of UTI, but again, *Enterococcus* was the most commonly isolated organism (25.7%), which was not covered by their recommended antibiotic. ERAS protocol was variably followed in this population. Kolwijck *et al.* reported similar findings in a retrospective cohort of 147 RC patients who received cefazolin plus metronidazole prior to incision. Postoperative infections were reported in 46.9%, including 18.4% with bacteremia, of which 67.9% had cultures positive for *Enterobacteriaceae*. In this study, the authors found the highest incidence of infections of postoperative day 4–5 and 8–10 and the second highest peak with ureteral stent removal, for which no prophylactic antibiotic was administered. In these two studies, orthotopic neobladder was associated with increased infections (OR: 5.03, $p<0.001$ and OR: 4.1, $p=0.03$, respectively).

Ghoreifi *et al.* assessed the efficacy of the perioperative antibiotic regimen at University of Southern California on postoperative UTIs following RC. Unlike prior studies, all patients were treated on the institutional ERAS protocol, which included 24-h perioperative antibiotics followed by suppressive antibiotics until removal of catheter/stents. UTI and urosepsis occurred in 36.1% and 7.13% of patients, respectively and the most commonly identified pathogens were *Candida* (25.57%) and *Escherichia coli* (22.16%). Among various suppressive antibiotic regimens, UTI (32.72 vs 45.24%, $p=0.04$) and urosepsis (5.25 vs 11.90%, $p=0.04$) were significantly reduced in patients who received fluoroquinolones. Increased UTI rates were associated with orthotopic neobladder (OR: 2.3, $p<0.05$) and perioperative transfusion (OR: 1.71, $p<0.05$). In summary, higher rates of infection by poorly covered organisms were reported with the original antibiotic protocol outlined in the 2013 ERAS guidelines. The timing and choice of antibiotic regimen is not well established in current ERAS protocols. Further work remains to be done to reduce infectious complications and readmissions associated with RC in the ERAS era.[103]

Pre-, intra-, and postoperative pain control

Contemporary ERAS protocols outline a multimodal postoperative analgesia regimen including nonopioid adjuncts such as intravenous/oral acetaminophen, ketorolac or ibuprofen, and gabapentin.[104,105] Intravenous and oral opioids may be reserved for breakthrough pain and effort is taken to transition to oral pain medication as early as possible. Significant advancements in

Table 2. Example of opioid-sparing pain management protocol.

Audenet *et al.*[113]	*Preoperative* Acetaminophen 1000 mg PO Gabapentin 600 mg PO Celecoxib 600 mg PO *Intraoperative* Regional TAP/quadratus lumborum block (30 ml 0.25% bupivacaine) under sedation/before surgery General Anesthesia Induction: ketamine 0.5 mg/kg, propofol 1.5–2.5 mg/kg During surgery: propofol 75–125 mcg/kg/min, ketamine 5–10 mcg/kg/h, dexmedetomidine 0.4 mcg/kg/h after bolus of 1 mcg/kg over 20 min Acetaminophen IV q6 h from preoperative oral dose Ketorolac 30 mg at end of procedure *Postoperative* Acetaminophen 1000mg IV Ketorolac 30 mg IV qh6 (held in renal insufficiency) Gabapentin 100 mg q8h Hydromorphone IV (for severe, refractory pain only)

pain management for RC have occurred since the publication of the 2013 ERAS guidelines.[7] In the original protocol, epidural analgesia was considered the "backbone" of multimodal opioid-sparing strategies, primarily based on colorectal and thoracic literature.[106] The evidence for neuraxial analgesia has not been replicated in the context of RC. In a systematic review, Rahman *et al.*[107] found that epidural analgesia was associated with a higher rate of complications, variable pain scores, and no improvement in LOS following RC.

Alternatively, increased use of regional anesthesia such as transversus abdominis plane (TAP) block and liposomal bupivacaine have been reported. TAP block refers to a technique in which local anesthetic is infused into the transverse abdominus plane, providing anesthesia to the anterior abdominal wall.[108] Roebuck *et al.*[109] conducted a retrospective cohort analysis of 178 RC patients managed on ERAS to assess the efficacy of surgeon-administered, laparoscopic-guided liposomal bupivacaine TAP blocks for postoperative analgesia. Liposomal bupivacaine (LB) is an extended-release formulation that may provide relief up to 72 h.[110] In colorectal studies, LB has been shown to reduce postoperative pain and opioid use, in line with ERAS goals.[111] Results showed significantly reduced POD 0-3 total opioid usage (106.4 vs 192.2 morphine milligram equivalents, $p = 0.004$) and mean LOS (5.6 vs 7.7 days, $p < 0.001$) in the TAP cohort. Pragmatically, Faraj *et al.*[112] demonstrated that the timing of TAP blocks, whether pre- or postoperative did not impact postoperative opioid usage ($p = 0.339$). Similarly, Chu *et al.*[104] retrospectively compared perioperative outcomes in patients who received incisional LB during closure and epidural catheter analgesia, most commonly with ropivacaine and fentanyl. Compared to epidural use, incisional LB was associated with reduced LOS (4.9 vs 5.9 days, $p < 0.001$), total opioid use (188.3 vs 612.2 oral morphine equivalents, $p < 0.001$), overall direct costs ($23,188 vs $29,628, $p < 0.001$), and time to diet advancement (1.6 vs 2.4 days, $p < 0.001$). Forty five percent of LB patients were reported to be opioid free postoperatively, compared to none in the epidural group.

In recent years, institutions have reported outcomes on prospective implementation of non-opioid pain protocols. Audenet *et al.*[113] found that 52 prospective patients treated with an opioid-sparing protocol including regional block had significantly decreased postoperative opioid use (2.5 vs 44 morphine milligram equivalents, $p < 0.001$), time to regular diet (4 vs 5 days, $p = 0.002$), LOS (5 vs 7 days, $p < 0.001$), and costs (8.6% reduction, $p = 0.032$) compared to 41 retrospectively matched patients treated prior to the implementation of a nonopioid protocol. Uniquely, this study removed intraoperative narcotic use, including fentanyl, and used non-narcotic alternatives for induction and anesthesia (Table 2). Greenberg *et al.*[114] implemented a "reduced opioid protocol," which included improved patient and provider education regarding non-opioid medications, in addition to a multimodal opioid-sparing regimen. Patients who followed the reduced opioid protocol had significantly decreased opioid use, both in the post-anesthesia care unit ($p = 0.003$)

and during the postoperative recovery (77% decrease in morphine equivalent dose, $p < 0.001$). Following colorectal precedents, significant improvements to multimodal opioid-sparing strategies have resulted in improved pain control and reduced LOS in patients undergoing RC. Still, there remains room to grow in the domain of patient and provider education, which can be difficult to standardize and quantify.

Potential challenges/barriers

Implementing pathways

Implementing ERAS pathways begins with provider acceptance of the evidence-based protocol. When the ERAS guidelines for RC were first introduced in 2013, surgeons were skeptical and slow to implement ERAS, citing lack of prospective RCTs.[115] In 2014, in a survey completed by 48% of 128 Society of Urologic Oncology fellowship-trained faculty, 64% of respondents classified themselves as practicing ERAS.[116] However, only 20% of respondents were practicing all 11 queried interventions. Results found that 13% were not practicing one intervention, 35% not practicing two, and 31% not practicing three or more. Between ERAS and non-ERAS providers, significant differences were reported in use of bowel preparation ($p = 0.001$), alvimopan ($p < 0.001$), and routine nasogastric decompression ($p = 0.007$). On analysis of outcomes, ERAS providers reported significantly reduced LOS (6.1 vs 7.2 days, $p = 0.02$), time to clear liquid diet ($p < 0.001$), and time to regular diet ($p < 0.005$). Most cited barriers to implementation of ERAS included lack of convincing evidence, followed by lack of belief in ERAS efficacy, and lack of institutional support. This study revealed the lack of consensus among urologic oncologists on ERAS adoption and practice of specific principles. Notably, implementation of an ERAS program can cost ~$100,000, which is offset by reduced resource utilization, but can further lead to reduced institutional support.[117] Since this publication, numerous studies have been published on the efficacy of ERAS on perioperative outcomes. It would be interesting to understand more updated practice patterns of urologic oncologists on attitudes toward ERAS and implementation of it.

Audit

Routine audit of compliance, outcomes, and cost-effectiveness is an integral component of the ERAS protocol for quality improvement.[7] Across surgical specialties, even modest improvements in compliance have been associated with improved perioperative outcomes.[118–120] In a multi-departmental study at an academic institution, Pickens *et al.*[121] found that increased ERAS compliance was associated with reduced postoperative LOS ($p = 0.004$) and 30-day survival ($p = 0.001$). Ghodoussipour *et al.*[122] conducted an internal institutional audit of 472 consecutive patients from 2013 to 2017. At onset of implementation, compliance, measured by a median composite compliance score (CSS), was 81%. The five-year median CSS increased to 88%. CSS was higher in younger ($p = 0.045$) and healthier ($p = 0.007$) patients who received more orthotopic diversions ($p < 0.0001$) and open surgery ($p < 0.0001$) and had shorter mean operative times ($p = 0.005$). Increased compliance ($\geqslant$ median of 88%) in 262 of 472 patients was associated with reduced median LOS ($p < 0.0001$), 30-day readmission rates ($p = 0.009$), and 90-day mortality rates ($p < 0.0001$). Most interestingly, no single ERAS item had an independent effect on outcomes. The authors propose that it is perhaps the additive effect of the multimodal ERAS interventions that most significantly impacts perioperative outcomes.

Recently, Albisinni *et al.* reported results from a multi-center survey distributed across 70 medium- to high-volume ERAS-practicing RC centers in 14 European countries. Expectedly, there was consensus (99%) that ERAS improved perioperative outcomes among adopters. However, 25% of centers had not performed an audit since implementation of ERAS. Moreover, 28.6% surgeons did not work with a referent anesthesiologist, which is critical for pre- and intraoperative ERAS care. Half of respondents (49%) believed that an external audit by an ERAS society member could be of benefit. ERAS targets with higher compliance (>90%) included preoperative counseling, avoidance of bowel preparation, thromboprophylaxis, prevention of intraoperative hypothermia, and removal of nasogastric tube. Lower compliance was reported for preoperative carbohydrate loading, opioid-sparing anesthesia, and regular auditing (<75%). Of note, auditing and opioid-sparing anesthesia were reported as the most complicated items to implement (14%). Overall, the greatest limitations to compliance were difficulty in changing habits (55%), followed by lack of communication across surgical and anesthesiology teams (33%), and absence of dedicated staff (28%).

Standardized and regular auditing identifies specific interventions with lower compliance, the first step to understanding and addressing challenges. While many institutions have overcome the initial barrier of implementation, continued audits and improvements are vital to ensuring translation to improved outcomes. Audits for novel interventions such as prehabilitation and immunonutrition should measure not only adherence, but feasibility of implementing such protocols. Finally, it should be noted that ERAS USA and ERAS Society have released the Reporting on ERAS Compliance, Outcomes, and Elements Research (RECOvER) checklist to improve the quality and reproducibility of ERAS reporting for future clinical studies. Systematic auditing and reporting will allow for improved data quality for meta-analyses and optimistically, increased participation in the ERAS protocol.

Limitations

This study was not conducted as a systematic review and is therefore open to potential bias. Although we focused on presenting RCTs and systematic reviews when possible, our findings may not be exhaustive of all evidence present for ERAS in RC patients.

Conclusion

The ERAS movement for RC patients has undergone significant advancements since original guidelines were released in 2013. Prospective RC-specific RCTs have been conducted to validate the efficacy of ERAS in improving perioperative outcomes, namely, bowel recovery and hospital LOS. Interventions such as epidural anesthesia that were once considered integral to managing postoperative pain, have been largely replaced by newer regional techniques. In addition, novel targets such as immunonutrition, prehabilitation, and alvimopan have been introduced. Nevertheless, consensus has not been achieved. Prospective investigations must continue to better understand the efficacy of individual ERAS items and standardize protocols to ultimately optimize patient care and experience.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Grace Lee: Data curation; Investigation; Project administration; Resources; Writing—original draft; Writing—review & editing.

Hiren V. Patel: Conceptualization; Data curation; Investigation; Project administration; Resources; Supervision; Writing—review & editing.

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