Enhanced Recovery After Surgery for Radical Cystectomy

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Abstract

Even with advances in perioperative medical care, anesthetic management, and surgical techniques, radical cystectomy (RC) continues to be associated with a high morbidity rate as well as a prolonged length of hospital stay. In recent years, there has been great interest in identifying multimodal and interdisciplinary strategies that help accelerate postoperative convalescence by reducing variation in perioperative care of patients undergoing complex surgeries. Enhanced recovery after surgery (ERAS) attempts to evaluate and incorporate scientific evidence for modifying as many of the factors contributing to the morbidity of RC as possible, and optimize how patients are cared for before and after surgery. In this chapter, we review the preoperative, intraoperative and postoperative elements of using an ERAS protocol for RC.

Keywords

Enhanced recovery after surgery · Radical cystectomy · Bladder cancer

1 Introduction

Bladder cancer is currently the fourth most common cancer and the eighth leading cause of cancer death among men in the USA [1]. It is predominantly a disease of the aging population, with a peaking incidence in the seventh decade when comorbid conditions are frequently present [1–3]. The overwhelming majority of bladder carcinomas (90%) are urothelial carcinomas, with 20% of this group presenting with muscle-invasive disease [4]. The gold standard treatment for muscle-invasive bladder cancer as well as high-risk non-muscle-invasive bladder cancers is radical cystectomy (RC).

Every year, approximately 10,000 RC operations are performed across the USA, [5]. The procedure along with pelvic lymph node dissection (PLND) and intestinal urinary diversion is among the most complex urological operations with many potential complications including postoperative cardiorespiratory failure, deep vein thrombosis, ileus, and metabolic derangement. Although advances in perioperative medical care, anesthetic management, and surgical techniques have lowered mortality to less than 3%, postoperative complications occur in 30–64% of patients and readmission are necessary in up to 30% of patients after RC [6–10]. Greater mortality and morbidity are observed in the elderly [11, 12]. Further, patients who undergo such a radical intervention are often admitted for long hospital stays as RC continues to be associated with a length of stay (LOS) of 8–11 days [7, 13]. Given the prolonged LOS, the high complication and readmission rates, there is much room for improvement in current RC care.

In recent years, there has been great interest in identifying multimodal and interdisciplinary strategies that help accelerate postoperative convalescence by reducing variation in perioperative care of patients undergoing complex surgeries. In the literature, multiple terms have been used to describe this concept: enhanced recovery after surgery (ERAS), enhanced recovery program (ERP), enhanced recovery after cystectomy (ERAC), fast-track surgery, accelerated recovery pathway, and care coordination pathway. However, common to all these approaches is the attempt to evaluate and incorporate scientific evidence for modifying as many of the factors contributing to the morbidity of RC as possible and optimize how patients are cared for before and after surgery [14].

Originating in the 1990s, the concept of fast-track surgery was created by Danish surgeon Henrik Kehlet, who studied the physiological stress response after colorectal surgery to determine if patients could easily be discharged much earlier than was traditionally practiced [15]. A separate group formally coined the term ERAS, describing it as a multimodal, perioperative approach that applies evidence-based interventions (including elimination of unnecessary measures) to modify the surgical stress response and shorten patient recovery time [16, 17]. Delivered by a team of professionals—anesthesia, surgeons, physiotherapists, and nurses—the concept has since been rolled out across many surgical specialties, creating procedure specific protocols in the fields of colorectal, urological, gynecological, vascular, and orthopedic surgery. The four keys to any ERAS protocol include: (1) appropriate preoperative assessment, patient identification and preparation prior to admission, (2) reducing physical stress of the operation—through a series of modifications to surgical and anesthesia intraoperative care, (3) a structured approach to the immediate postoperative care, including pain relief and nutrition, and (4) early mobilization.

Within the urologic literature, ERAS for RC has faced criticism for overreliance on retrospective evidence, use of higher level but not necessarily applicable colorectal data, and inconsistent application of enhanced recovery principles across protocols [14]. Most studies examining enhanced recovery for RC have been nonrandomized, small, and retrospective. In this chapter, we review the current evidence for using an enhanced recovery protocol for RC.

Table 1 Preoperative aspects of ERAS for radical cystectomy

Preoperative ERAS elements
Patient counseling and education • Provide leaflets or multimedia information • Set expectations • Discharge planning • Stoma education
Preoperative medical optimization • Optimize medical diseases • Encourage smoking and alcohol cessation • Physical conditioning (prehab) • Improve nutritional status
Avoid mechanical bowel preparation
Avoid fasting
Carbohydrate loading
Alvimopan administration
Pre-anesthetic medication • Avoid long active sedatives
Thromboembolic prophylaxis • Low-molecular weight or unfragmented heparin • Compression stockings and intermittent pneumatic compression devices

2 Preoperative ERAS Elements

At the core of any ERAS protocol is good communication between the patient, urologist, urology stoma nurse specialist, anesthetist, and general practitioner. Before proceeding with RC with any patient, it is important to identify patients at high risk of postoperative morbidity, as it helps guide the risk versus benefit ratio of operative intervention and furthermore determine their postoperative care requirements. One should perform a thorough history and identify preexisting cardiovascular and respiratory disease by simple self-assessment questionnaires. These can be used to measure a patient's functional capacity and get a rough estimate of a patient's peak oxygen uptake. One metabolic equivalent (MET) represents the oxygen consumption of an adult at rest (i.e., 3.5 ml/kg/min), and varying degrees of exercise are designated a number of METs. Patients being considered for major surgery should be able to perform >4 METs, which is roughly the equivalent exertion of climbing one flight of stairs [18] (Table 1).

2.1 Preoperative Counseling and Education

There is no evidence that preoperative patient information and counseling improves outcomes after RC [17]. However, detailed information given to patients preoperatively may diminish fear and anxiety and enhance postoperative recovery and accelerate hospital discharge [19, 20]. Personal counseling, leaflets, or multimedia information containing explanations of the procedure along with tasks that the patient should be encouraged to fulfill may improve perioperative feeding, early postoperative mobilization, pain control, and respiratory physiotherapy [21–24]. In the colorectal literature, lack of adequate preoperative stoma education has been shown to be an independent risk factor for delayed discharge in patients on ERAS pathways [25]. Additionally, the patient should be actively engaged by preoperatively meeting members of the entire surgical team [26].

2.2 Preoperative Medical Optimization

Optimization of medical diseases (diabetes, hypertension, and anemia) along with physical exercise and cessation of smoking, drugs, or alcohol are preoperative conditioning measures that have been identified as reducing post RC complication [12, 27]. Alcohol abusers have a two-to-threefold increase in postoperative morbidity with the most frequent complications being bleeding, wound complications, and cardiopulmonary complications. One month of preoperative abstinence reduces postoperative morbidity by improving organ function [28, 29]. Another patient factor that has a negative influence on recovery is smoking. Current smokers have an increased risk for postoperative pulmonary and wound complications [30]. One month of abstinence from smoking is required to reduce the incidence of complications [30, 31]. However, aside from a retrospective cohort analysis identifying most of these risk factors, there is no other available evidence in urologic literature showing that their correction improves outcome [12, 17].

Physical conditioning (prehab) and muscle training may improve recovery rates. Several randomized controlled trials across various surgical fields (general abdominal surgery, cardiothoracic surgery, and orthopedic surgery) have investigated the role of preoperative physical conditioning on surgical outcomes [32–38]. Although there were varying degrees of improvement in physiological function and surgical recovery, only one study found improvement in physiological function that correlated with improved surgical recovery [24].

Studies have also demonstrated correlation between markers of malnutrition and adverse outcomes in RC [39]. In a dataset of patients undergoing gastrointestinal cancer surgery, poor nutritional status was directly correlated with extended LOS and increased risk of complications [40]. In RC patients, Gregg et al. reported nutritional deficiencies in almost 20% of patients and suggested severely malnourished patients should be treated for 10–14 days prior to surgery in order to decrease complications, even if surgical delay is implied [39]. Treatment to improve preoperative nutrition status includes nutritional supplements and immune-enhancing nutritional supplements (arginine, glutamine, nucleic acid, omega-3 fatty acids, antioxidants), which allow for the up-regulation of pro- and anti-inflammatory compounds. Bertrand and colleagues demonstrated that seven days of oral immune nutritional support intake preoperatively reduced postoperative complications, LOS, postoperative ileus, and pyelonephritis in RC patients [41].

2.3 Oral Mechanical Bowel Preparation

In colonic surgery, mechanical bowel preparation can dehydrate patients and cause electrolyte imbalance, physiological stress, and prolonged ileus. A meta-analysis including 5000 patients undergoing elective colorectal surgery identified no benefits for performing mechanical bowel preparation, concluding mechanical bowel preparation may be associated with greater morbidity, particularly anastomotic leakage and wound complications [42].

In the urologic literature, Tahibi and colleagues prospectively found no difference in morbidity or LOS when comparing 32 RC without bowel prep to 30 patients that had undergone standard 3-day mechanical bowel prep [43]. Similarly, Xu et al. found no statistical difference in morbidity, LOS, or time to first bowel movement by randomizing 86 patients [44]. Other randomized controlled trials in urologic literature have shown no differences in recovery of bowel function, time to discharge, or overall complication rates despite differences in design and heterogeneity of the “no bowel prep” arm (no bowel prep versus limited bowel versus enema only) [45, 46]. Currently, there is a lack of evidence from large randomized controlled trials to support using bowel preparation in RC patients.

2.4 Preoperative Fasting

Fasting from midnight has been standard practice in the belief that this secures an empty stomach and thereby reduces the risk of pulmonary aspiration in elective surgery. However, there has never been any scientific evidence behind this dogma. A Cochrane review of 22 RCTs showed that fasting from midnight neither reduce gastric content nor raises the pH of gastric fluid compared with patients allowed free intake of clear fluids until 2 h before anesthesia for surgery [47]. Equally, intake of clear fluids >2 h before surgery does not increase the prevalence of complications. Based on available evidence, the European Anesthesia Guidelines state that clear fluids are permitted up to 2 h and solids foods up to 6 h before the induction of anesthesia [48].

2.5 Preoperative Carbohydrate Loading

While there is no study evaluating carbohydrate loading in RC patients, it has been shown that such preoperative loading decreases thirst, reduces insulin resistance, and helps maintain lean body mass and muscle strength in colorectal surgery [27]. A meta-analysis of preoperative liquid carbohydrate treatment in open abdominal surgery patients revealed a significant reduction in LOS compared with controls [49]. In a double-blinded randomized controlled trial, Hausel and colleagues demonstrated reduced incidence of postoperative nausea and vomiting in patients receiving carbohydrate loading [50]. In summary, carbohydrate loading is a standard-of-care technique in ERAS programs that is safe in diabetic populations and can be given up to 2 h before surgery [51].

2.6 Preoperative Alvimopan Administration

As the most common complication following RC, postoperative ileus is a particular focus of ERAS protocols. Postoperative ileus can impair a patient's nutritional status, increase the probability of morbidity, and increase LOS as well as costs [6, 7, 12, 52, 53]. The use of alvimopan has been associated with a reduced LOS and faster recovery of bowel function after abdominal surgery and RC [54, 55]. In the urologic literature, one of the few randomized controlled trials evaluating an individual component of enhanced recovery following cystectomy was recently published by Lee et al. regarding the use of alvimopan (a peripherally acting μ-opioid receptor antagonist) and its impact on bowel recovery [55]. In this multicenter randomized controlled trial, the alvimopan cohort had a shorter LOS (7.4 vs. 10.1 days), passed a bowel movement more quickly (5.5 vs. 6.8 days), and had 20% fewer episodes of postoperative ileus-related morbidity (nasogastric tube reinsertion, prolonged stay, or readmission due to ileus). It should be noted that the study included a high proportion of patients who underwent open RC, as minimally invasive surgery using multimodal analgesia has shown lower morphine requirements than open surgery [56, 57]. However, positive effects of alvimopan administration in minimally invasive surgery have also been demonstrated. In a series of 117 patients undergoing robotic RC, Tobis and colleagues showed alvimopan administration appeared to reduce the time to return of bowel function (5 vs. 6 days) and initiation of diet (6 vs. 7 days) following robotic RC [58].

2.7 Pre-anesthetic Medication

A large proportion of patients are undergoing RC experience perioperative psychological distress [59]. Preoperative education can reduce patient anxiety to an acceptable level without the need for anxiolytic medication. However if pre-medication with anxiolytics is required, long-acting sedative pre-medication should be avoided, especially in elderly patients, for up to 4 h post-surgery as it affects immediate postoperative recovery by impairing mobility and oral intake [17, 27]. Short-acting benzodiazepines such as midazolam are preferred, if necessary, to reduce anxiety and facilitate patient positioning [17, 27].

2.8 Thromboembolic Prophylaxis

Currently, no randomized control trial or prospective study has compared complication rates with and without deep vein thrombosis prophylaxis in RC patients. However, as the incidence of clinically significant deep vein thrombosis after cystectomy is estimated at 4%, thromboembolic prophylaxis using low-molecular weight or unfragmented heparin should be used to reduce the risk of symptomatic thrombosis [60]. Additionally, compressive stockings and intermittent pneumatic compression devices can further decrease this risk.

Regarding the duration of thromboembolic prophylaxis in the postoperative setting, Bergqvist and colleagues observed a significant decrease in the post-hospitalization venous thromboembolism rate among abdominal and pelvic surgical oncology cases in which low-molecular-weight heparin prophylaxis was continued for 19–21 days after a standard in-house anticoagulation regimen compared with placebo [61].

3 Intraoperative ERAS Elements

The intraoperative period is a critical time in the ERAS pathway, with specific considerations from both the anesthetic and surgical perspectives (Table 2).

3.1 Antimicrobial Prophylaxis and Skin Preparation

As cystectomy is considered a "clean-contaminated" surgery, antibiotic prophylaxis for patients undergoing RC should cover against aerobic and anaerobic organisms. The European Association of Urology guidelines suggest that antibiotics should be administered no earlier than 1 h before surgery and continued for up to 24 h and extending to 72 h for patients with specific infection risk factors or prolonged operations (>3 h). The National Surgical Infection Prevention Project also advised that antibiotics should be administered before skin incision and less than 1 h before surgery [62]. Although the best antibiotic regimen is unclear and likely depends on local antibiotic-resistance profiles, the American Urological Association guidelines recommend a second-generation or third-generation cephalosporin or a combination of gentamicin and metronidazole for 24 h perioperatively if there are no patient risk factors.

Regarding the optimal skin preparation, several ERAS guidelines recommend skin preparation prior to surgery using a chlorhexidine–alcohol scrub to prevent surgical site infections (SSIs) [17, 27]. A study comparing different types of skin

Table 2 Intraoperative aspects of ERAS for radical cystectomy

Intraoperative ERAS elements
Antibiotic prophylaxis and skin preparation
Anesthetic protocols • Use of thoracic epidural • Neural blockade • Minimal opioid use • Prevention of intraoperative hypothermia • Individualized goal-directed fluid therapy
Minimize incision (minimally invasive approach)
Drain strategy

cleansing showed that the overall prevalence of surgical site infection was 40% lower in a concentrated chlorhexidine–alcohol group than in a povidone-iodine group [63]. However, there is a risk of fire-based injuries and burn injuries if diathermy is used in the presence of alcohol-based skin solutions [64].

3.2 Anesthetic Protocols

Evidence from colorectal and RC studies suggest that ERAS anesthetic protocols should encompass the use of thoracic epidural (T9-11), minimal opioid use, replacing it with fentanyl-based short-acting opioids, and strategies for prevention of hypothermia, hypoxemia, and hypovolemia [65].

No prospective single-intervention study has been conducted to assess epidural analgesia in the perioperative management of RC; however, there has been strong evidence shown in open colorectal surgery that epidural analgesia reduces the stress response to surgery, provides superior pain relief, reduces postoperative complications, and accelerates functional recovery [66]. In colorectal surgery, the administration of thoracic epidural anesthesia is widely recommended to reduce LOS and postoperative ileus compared with patient-controlled analgesia [27] (Table 3).

Recent ERAS society cystectomy recommendations strongly encourage the use of a thoracic epidural for 72 h after surgery, as the benefits listed are key components in delivering an effective ERAS protocol [17]. Epidural analgesia in combination with paracetamol and nonsteroidal anti-inflammatories (where there are no contraindications) reduces and often removes the need for systemic opioid analgesia, and its associated side effects of bowel dysfunction, respiratory depression, and nausea [18]. In open RC, various studies have demonstrated the successful use of epidural anesthesia or patient-controlled analgesia and rectus sheath catheters; however, no prospective studies have compared these anesthetic protocols in RC surgeries [26, 67–69].

Table 3 Postoperative aspects of ERAS for radical cystectomy

Postoperative ERAS elements
Avoid postoperative nasogastric intubation
Early oral intake
Early mobilization
Ureteral stenting
Gum chewing
Multimodal opioid-sparing analgesia combined with regional or local anesthesia
Discharge planning

3.3 Prevention of Intraoperative Hypothermia

Perioperative hypothermia (core body temperature of less than 36 °C), which is common during major surgery, may promote surgical wound infection by triggering thermoregulatory vasoconstriction [70]. This subsequently decreases subcutaneous oxygen tension and reduces the strength of the healing wound by reducing the deposition of collagen. Hypothermia also directly impairs immune function. In colorectal surgery, avoiding intraoperative hypothermia has shown to decrease the incidence of infectious complications, help protect against perioperative coagulopathy, and reduce LOS [26, 70]. Given the similar physiopathology resulting in impaired thermoregulation in cystectomy procedures, maintaining normothermia is strongly warranted [17]. The most effective warming strategies are forced-air warming blankets and warmed IV fluids [70].

3.4 Perioperative Fluid Management

Fluid management in patients undergoing RC can be challenging as urine output is often not measurable intraoperatively. Both fluid excess and hypovolemia can provoke splanchnic hypoperfusion, which can then result in ileus, increased morbidity and longer LOS [71]. Primary research efforts in perioperative care have focused on determination of what constitutes optimal fluid management during surgery.

Goal-directed fluid therapy (GDFT) using cardiac output monitors, such as a transesophageal Doppler device to guide fluid and inotropic therapy, is one such strategy. Used in conjunction with invasive arterial pressure monitoring and central mixed venous oxygen saturation from a central venous pressure line, intraoperative individualized fluid therapy aims to optimize cardiac output, and therefore tissue perfusion and oxygenation. By optimizing blood flow to tissues, GDFT aims to improve gut perfusion thereby reducing the incidence of hypoperfusion and therefore occult bowel ischemia and postoperative ileus and allows the anesthetists a better guide as to how the patient is responding to the significant fluid shifts that occur during major surgery [71].

In colorectal surgery, GDFT has been shown to improve outcomes and reduce complication rates and LOS [71, 72]. However, these studies evaluated GDFT against standard fluid management techniques, and the comparison groups often had fluid overload or unwarranted restrictions [71, 72]. In a small randomized controlled trial, Pillai and colleagues investigated the effects of GDFT in RC patients and concluded that patients who underwent GDFT had a reduced incidence of ileus and of nausea and vomiting at 24 and 48 h [73]. Large prospective studies are needed in urology to compare restricted, balanced, and GDFT in patients undergoing RC. However, it is reasonable to assume that patients undergoing major or high-risk surgery need a dedicated, individualized goal-directed fluid management run by an experienced anesthetist to ensure adequate tissue perfusion, and a Doppler-guided strategy may prove a valuable adjunct in these cases [17].

3.5 Minimally Invasive Approach

Another factor contributing to the morbidity of RC is the complexity of the procedure itself. It involves multiple surgeries in one: deep pelvic dissection to remove the bladder, lymphadenectomy, and extensive bowel manipulation for the urinary diversion. With the majority of RC being performed by high-volume surgeons, innovation in surgical performance has focused on operative approach (robotic versus open). By offering a minimally invasive surgery over an open approach, the hope is to decrease the patients' inflammatory response and reduce the risk of postoperative ileus, complications, and duration of hospital stay. Robotic surgery, however, is not without its physiological challenges. It requires a prolonged period of steep Trendelenburg position, together with pneumoperitoneum, **and** can produce dramatic physiological derangement, particularly in the elderly populations with multiple comorbidities who present for RC.

First reported in 2003 as a feasible approach, robotic RC requires smaller incisions, reduces analgesic use, reduces bowel handling, and decreases blood loss [57, 74]. A recent meta-analysis comparing open to robotic RC found robotic RC was associated with less blood loss and shorter LOS [75]. However, open RC demonstrated a clear advantage to robotic RC in terms of reduced operating time. The International Robotic Cystectomy Consortium reported on over 1000 patients and demonstrated 30-day complication rate of 41% (61% were low-grade complications) with similar oncological outcomes to the open approach and dependent on surgeon's experience [76]. Three randomized trials have been published comparing open RC with robotic RC, with strikingly similar results to each other [57, 77, 78]. Robotic RC has been shown to improve some perioperative parameters such as estimated blood loss and LOS, but in all three studies no significant differences were found in complication rates. A systematic review comparing RARC with ORC similarly concluded that although RARC can be performed safely, complication rates remain significant [79].

When looking at oncologic outcomes of the minimally invasive approach, Yuh and colleagues performed a systematic review of over 100 papers and found 5-year oncologic outcomes similar between robotic RC and open RC [80]. Additionally, Snow-Lisy and colleagues reported on a cohort of 120 patients with 10-year follow-up and proved no differences in overall survival, cancer-specific survival, and recurrence-free survival when comparing the minimally invasive RC approach to the open approach [81].

Another variable often thought to contribute to complications and readmissions of RC is the type of urinary diversion the patients receives. Choice of urinary diversion depends largely on oncological eligibility, patient comorbidities, surgeon preference, and patient preference. Nazmy and colleagues stratified complications by urinary diversion type in robotic RC patients, and despite the selection of a more comorbid population for ileal conduit diversion, patients with ileal conduit diversion had a decreased likelihood of complications compared to patients with Indiana pouch and orthotopic bladder substitute diversion [82]. However, other studies have shown comparable rates of 90-day complication rates between ileal conduits and neobladders, suggesting the choice of diversion may contribute less to the morbidity of the procedure than previously thought [83–85]. However, the impact of the choice of urinary diversion remains to be completely defined.

It aims to further reduce the invasiveness of the procedure, intracorporeal urinary diversion (ICUD) has been performed in certain centers. Early, small studies comparing ICUD with extracorporeal urinary diversion have it to be safe and suggest less gastrointestinal complications and less overall 90-day complications [86]. However, the consortium paper had notable limitations including its retrospective, non-uniform data collection; lack of complication/readmission data in 118 patients (12.6%); and that the majority of ICUDs were ileal conduits which may have confounded results with regard to gastrointestinal and overall complications. Overall, ICUD remains a challenging aspect of the robotic RC procedure and should remain in the hands of a few very high-volume centers.

Despite the inclusion of the minimally invasive approach in the ERAS Society guidelines published by Cerantola and colleagues [17], the superiority of robotic versus open cystectomy remains to be demonstrated definitively. Future high-quality, high-volume randomized, controlled studies such as the prospective randomized open versus robotic cystectomy (RAZOR) trial examining this question is accruing and should help in reaching definitive conclusions on the role of robotic RC [87].

3.6 Resection Site Drainage

Regardless of the surgical approach, the use of intraabdominal drains continues to be debated. In colorectal surgery, meta-analyses have concluded that intraabdominal drains confer no benefits in terms of anastomotic dehiscence, wound infection, reoperation, extra-abdominal complications, or mortality [88]. For RC and urinary reconstruction, even though observational studies have shown no detriment to omission or early removal of the drain, or to shortening the drain into a stoma bag [4, 89, 90], the subject remains controversial given the risk of urinary leakage within the peritoneal cavity.

4 Postoperative ERAS Elements

Historically, RC patients were kept nothing by mouth, with a nasogastric tube (NGT), bedbound, and had a prolonged hospital stay. However, with ERAS, almost the direct opposite has become the standard of care, owing to the consideration of a number of postoperative factors.

4.1 Urinary Drainage

In a small randomized controlled trial, Mattei and colleagues investigated the effect of time-to-stent removal in ileal bladder substitute and ileal conduit patients [91]. The study compared patients whose stents were removed directly following ureteroileal anastomosis with those whose stents were removed 5–10 days after surgery. Stenting was associated with improved upper tract drainage, lower postoperative ileus, and reduced rate of metabolic acidosis [91]. However, the best time for removal of a ureteric drain/stent after RC has not been clearly established [26].

4.2 Nasogastric Intubation

Many centers now remove NGTs at the end of surgery in RC cases, to avoid delayed gastric emptying, nausea, and vomiting that would otherwise delay patient mobilization and therefore participation in an ERAS protocol. Extrapolation is possible from level 1a evidence relating to colorectal surgery to show NGTs are not only unnecessary, but also detrimental. In a meta-analysis of 33 randomized controlled trials including 5240 patients on the use of NGT decompression after abdominal surgery, patients not having routine NGT use had an earlier return of bowel function ($p < 0.00001$) and decrease in pulmonary complications ($p = 0.01$). [92] Although most data are associated with colorectal surgery, numerous reports suggest relevance to urological procedures [93, 94].

4.3 Prevention of Postoperative Ileus

With respect to the prevention of postoperative ileus, specific treatments such as preoperative alvimopan, fluid monitoring, performing a minimally invasive approach, and ureteral stenting have already been discussed in this review. Gum chewing is a form of sham feeding that has been studied specifically in the context of open and robotic RC in two trials that showed a significantly decreased time to flatus and first bowel motion in both open and robotic groups with gum chewing [95, 96]. Despite these findings, there was no significant difference in LOS and postoperative complications. Nonetheless, gum chewing should be started on postoperative day 1 and continued through the hospital course in order to reduce postoperative ileus.

Prokinetic agents, such as erythromycin and metoclopramide, have shown no benefit in decreasing time to flatus or first bowel movement [97, 98]. However, in light of this evidence, metoclopramide was removed from one of the most established ERAS protocols for RC, resulting in a significant increase in postoperative nausea and vomiting and prompting its reinstitution to facilitate tolerance of early enteral intake [99, 100].

Prophylactic oral laxatives have been recommended after surgery, as they are associated with an earlier return to normal bowel function and a reduction in time to defecation [17, 27, 101]. However, no prospective studies have systematically evaluated the benefits of oral laxatives in colorectal or urological surgery with or without the use of ERAS pathways [26].

4.4 Early Feeding

Contrary to conventional surgical dogma that feeding should begin only after the return of bowel function (passage of flatus or stool), early feeding can reduce insulin resistance, with beneficial effects on muscle function, wound healing, and sepsis [102]. Although no evidence supporting an early oral diet exists for RC specifically, Behrns and colleagues found that beginning an oral diet with clear liquids on postoperative day 2 and progressing quickly to a regular diet decreased LOS without increasing postoperative morbidity in elective intestinal surgery [103]. Similarly, Fearon and colleagues used a multimodal approach, including early oral feeding postoperatively, carbohydrate and fluid loading preoperatively, and decreased LOS from 10 days to 7 days in patients undergoing elective colorectal surgery [104]. Additionally, a meta-analysis of major abdominal surgery (not including RC) concluded that pneumonia, anastomotic dehiscence, wound infection, and mortality were all less likely with early feeding. Secondary end points, including time to flatus, time to bowel motion, and LOS, were all also improved by early feeding [105]. Given the evidence presented above, prevalence of malnutrition in patients undergoing RC, and lack of evidence against it, early oral feeding should be encouraged postoperatively. However, a risk of early postoperative oral intake is vomiting, and active interventions, such as scheduled anti-emetics, chewing gum, cholinergic stimulants, laxatives, prokinetic agents, and limitations on narcotic administration, must be instituted alongside early oral intake to prevent postoperative nausea and vomiting.

In addition to early feeding, postoperatively intravenous fluid should be minimized to prevent fluid overload and bowel edema [100]. If normovolemic hypotension is seen with thoracic epidural anesthesia, it should be corrected with vasopressors instead of intravenous fluid [106]. However, if parenteral fluids are needed, balanced crystalloid such as Ringer's lactate solution should be used instead of normal saline to protect against electrolyte disruption (i.e., hyperchloremic metabolic acidosis) [107].

4.5 Postoperative Analgesia

With the aim of providing effective pain relief and minimizing adverse effects, especially those that are associated with opioids, multimodal opioid-sparing analgesia combined with regional or local anesthesia is a key component of ERAS. The use of thoracic epidural analgesia with wound infiltration or rectus sheath cannulas is recommended for 24–72 h post-surgery [108]. Ventham and colleagues reported that subfascial wound catheter placement significantly improved analgesia and diminished opioid requirements [109].

The use of regular intravenous or oral paracetamol as well as nonsteroid anti-inflammatories (NSAIDs) have been a well-documented aspect of many RC ERAS protocols [67–69]. Specifically, the NSAID ketorolac, when used in conjunction with morphine, has been found to decrease the rate of postoperative ileus by over fivefold in a series of colorectal surgery patients [104]. However, concerns exist regarding the cardiac toxicity and anastomotic dehiscence with NSAID use [110, 111].

Overall, few studies (and no prospective studies) have examined the adaptation of multimodal opioid-sparing analgesia to RC, and in the future, randomized controlled trials are needed to compare the effects of these pain medications on RC patients.

4.6 Early Mobility

Appropriate analgesia facilitates early postoperative mobility, which in turn may counteract insulin resistance, reduce thromboembolic events and chest infection rates, increase muscle strength, and possibly reduce ileus [27, 112]. In an ERAS series of laparoscopic colorectal surgery patients, it was shown that early mobilization was associated with improved outcomes and lack of adherence to early mobilization protocols was associated with longer LOS [113]. Recently, Jensen and colleagues showed that in a population of 57 RC patients, increased mobilization can improve the ability of patients to perform activities of daily living [114]. However, no ERAS studies on exclusively RC patients suggest that early mobilization plays a role in decreased morbidity or LOS following surgery. Nonetheless, early ambulation is widely practiced in established RC ERAS protocols. In a review of 10 single-center studies, early mobilization was the only intervention unanimously used by the reviewed centers [14].

4.7 Discharge Criteria

ERAS programs recommend that discharge should only occur when patients have resumed adequate oral intake and normal bowel function with effective oral pain management and when no other clinical or biochemical concerns remain, including stoma or neobladder competency [26]. In regard to stoma care, nurse specialists play a key role in engaging patient participation in the initial perioperative period. One center reported that early visits, from day one, ensure patients feel supported in coming to terms with the appearance of their stoma, and from day two, patients are encouraged to engage in their stoma care, for example changing the stoma pouch

[115]. After discharge, patients should feel well supported and routine telephone consultation, as well as the provision of an emergency patient hotline, has been suggested as a standard of care [89, 90].

4.8 Quality of Life

Quality of life measures have not always been documented with conventional care. Within ERAS protocols, some have evaluated their impact on quality of life [116, 117]. In a systematic review of various abdominal surgeries (not including cystectomy), Stowers et al. observed no improvements in quality of life, between ERAS and standard of care [116]. However, Karl and colleagues randomized patients to conventional care or ERAS for RC patients and assessed outcomes according to European Organization for Research and Treatment of Cancer (EORTC) quality of life (QLQ-30) questionnaires [117]. When analyzing the emotional functioning score exclusively, they found a stable score during hospitalization in the conventional care group, whereas continuous improvement was found in the ERAS group. In RC patients, this study was the first of its kind demonstrating an emotional benefit for patients undergoing an ERAS protocol [117].

5 Future Considerations for ERAS

As previously mentioned, ERAS for RC has faced criticism for overreliance on retrospective evidence, use of higher level but not necessarily applicable colorectal data, and inconsistent application of enhanced recovery principles across protocols [14]. In a summary of the current evidence behind ERAS for RC, Cerantola and colleagues proposed 22 core ERAS elements, and of those 22 elements, the highest quality evidence came from the colorectal literature [17]. Given the oncological, procedural (prolonged extent and duration of spillage of urine as well bowel contents within the peritoneal cavity), and morbidity differences between colorectal and cystectomy surgery, there is an urgent need to evaluate ERAS pathways in patients undergoing urological surgery, specifically RC.

Several groups have published the results of their proposed ERAS protocols in RC (Table 4) [4, 52, 69, 90, 99, 117–126]. Although most demonstrate improved postoperative recovery for patients, the ERAS protocols themselves are quite varied with only a small portion of series implementing more than 50% of the 22 recommended ERAS principles. The inconsistency in enhanced recovery protocols in urology has led to some confusion as to which elements of these protocols are truly necessary and which make the biggest difference for patients' recoveries after RC. Nonetheless, the interventions used most frequently (in >50% of studies) in most published series includes the circumvention of mechanical bowel preparation and routine NGT placement, preoperative carbohydrates loading, the use of epidural

Table 4 Recent publications on enhanced recovery after surgery (ERAS) protocols for radical cystectomy (RC)

Series	Year	Study type	Comparative control group included	Number of ERAS patients	Robotic RC included	Number of ERAS items
Maffezzini et al. [52]	2007	Retrospective	No	68	No	9
Arumainayagam et al. [119]	2008	Retrospective	Yes	56	No	9
Pruthi et al. [100]	2010	Retrospective	No	100	No	8
Saar et al. [120]	2013	Prospective	Yes	31	Yes	9
Mukhtar et al. [4]	2013	Prospective	Yes	51	No	14
Daneshmand et al. [69]	2014	Prospective	Yes (Historical)	110	No	11
Dutton et al. [90]	2014	Retrospective	No	165	No	19
Guan et al. [121]	2014	Retrospective	Yes	60	No	7
Karl et al. [118]	2014	Prospective	Yes (RCT)	62	No	7
Smith et al. [91]	2014	Retrospective	Yes	64	No	7
Cerruto et al. [122]	2014	Prospective	No	31	No	17
Persson et al. [123]	2015	Retrospective	Yes	31	No	13
Koupparis et al. [124]	2015	Retrospective	Yes	102	Yes	10
Xu et al. [125]	2015	Retrospective	Yes	124	No	17
Collins et al. [126]	2016	Prospective	Yes	135	Yes	20
Chipollini et al. [127]	2017	Retrospective	Yes	112	No	11

RCT—randomized controlled trial

analgesia, thromboembolic and antimicrobial prophylaxis, opioid-sparing analgesia, judicious fluid management, prevention of intraoperative hypothermia, early mobilization and early oral feeding. In addition, several protocols require a fair measure of coordination on the part of the clinical care team to ensure compliance. For example, Daneshmand and colleagues were able to decrease LOS from 8 to 4 days without impacting complication rates (65% vs. 64%) or readmissions (21% vs. 18%) in a series of 126 ERAS patients after RC. However, the protocol involved measures such as paraincisional subfascial catheters for continuous local anesthesia, and coordination for patients to receive 1 L intravenous fluid every other day after hospital discharge to preempt dehydration (a common cause for readmission after RC). Such elements may be difficult to reproduce with 100% compliance.

ERAS protocols have been adopted in many surgical specialties, particularly colorectal surgery, with improvements in mortality and morbidity. However, urologists have been slower to embrace ERAS than other surgical subspecialties. A survey was sent to Society of Urologic Oncology members with a self-identified special interest in bladder cancer, asking whether they consider themselves ERAS adapters and inquiring specifically about adherence to seven components of virtually all ERAS protocols (comprehensive preoperative education, bowel preparation avoidance, NGT avoidance, intraoperative normothermia, opioid avoidance, early ambulation, and early feeding) [127]. While nearly half of the bladder cancer surgeons contacted responded to the survey, and 64% of respondents considered themselves to adhere to ERAS principles for RC, only 20% practiced all 7 interventions. The most commonly cited reasons for non-adopting ERAS protocols were the lack of convincing evidence, the belief that ERAS does not work, and lack of institutional support. With the exception of specific medications whose availability or ease of use may differ by hospital, adopting ERAS principles (like omitting a bowel preparation or avoiding opioid analgesics) requires a change in practice patterns. The successful implementation of an ERAS program requires full commitment and support of the involved parties and to convince urologists to change their long-established ways for taking care of some of their sickest patients. There will need to be a high-quality, prospective study to provide convincing evidence of the utility of ERAS for RC [14].

6 Conclusion

In summary, even with the limitations of ERAS regarding the generalizability of urologic evidence, a tipping point is being reached where it is hard to deny the growing evidence showing that ERAS protocols have a positive impact on patient recovery. However, it remains to be determined exactly which elements of ERAS have the most substantial impact. In the future, high-quality prospective, randomized controlled multicenter studies where components can be isolated or added sequentially are needed to validate the different elements of ERAS protocols.

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