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Review Article
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Enhanced Recovery after Surgery Protocol for Patients Undergoing Radical Cystectomy

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Abstract

Radical Cystectomy (RC) is considered the most effective treatment for muscle-invasive bladder cancer. However, despite advancements in perioperative care, anesthesia management, and surgical techniques, RC is associated with a high rate of complications and prolonged hospitalization. As a result, there is growing interest in developing comprehensive approaches involving multiple disciplines to enhance postoperative recovery and reduce variations in perioperative care for complex surgeries.

The implementation of Enhanced Recovery After Surgery (ERAS) protocol has shown promising results in reducing gastrointestinal complications and shortening hospital stays for RC patients, without increasing readmissions or overall morbidity. Ongoing research is focusing on incorporating scientific data into the ERAS program to modify variables that contribute to RC complications, and to enhance both pre- and postoperative patient care.

Utilizing ERAS protocols in RC patients can significantly improve postoperative recovery and reduce morbidity rates. However, further research is needed to evaluate the effectiveness of integrating scientific data into the ERAS program, and to identify additional strategies for enhancing pre- and postoperative patient care.

The purpose of this review is to provide a summary of the key components of an ERAS protocol for patients undergoing RC, including the preoperative, intraoperative, and postoperative phases, as well as explore future research possibilities. A thorough literature search was conducted to identify studies demonstrating the effectiveness of ERAS protocols in improving outcomes for RC patients. Additionally, ongoing studies investigating the integration of scientific data into the ERAS program to address factors contributing to RC complications were examined.

Keywords: Bladder cancer; Enhanced recovery after surgery; Radical cystectomy

Introduction

Radical cystectomies consist of three types of surgery: Removal of the bladder and surrounding tissues, pelvic lymph node dissection, and urinary diversion. These procedures are performed together, resulting in a long operative time and often requiring a lengthy hospital stay (8 to 9 days in the United States and 15 to 20 days in Europe) [1]. Short- and long-term complications, as well as mortality rates, are high following this surgery, with rates of approximately 27% to 32%, 64%, and 1.5% to 5%, respectively [2-5].

A multidisciplinary approach has recently gained significant attention as a means of improving patient treatment and recovery after complex surgeries with a high risk of complications. This approach, known as the Enhanced Recovery after Surgery (ERAS) protocol, has been shown to lead to improved treatment outcomes in a variety of surgical fields. The benefits of ERAS programs have been most pronounced in patients with complex surgeries who require multiple teams and experience high rates of readmission and a prolonged hospital stay.

While there are limitations to analyzing surgery-related research due to the high number of confounding variables, a growing body of evidence suggests that standardized pre- and postoperative treatment methods based on evidence improve clinical outcomes.

In the field of urologic oncology, the application of ERAS programs is given priority in the context of radical cystectomies, which are complex surgeries with a high frequency of postoperative complications. This study aimed to evaluate the effectiveness of ERAS programs and interventions in radical cystectomy and provide guidance for future directions by summarizing the evidence for

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each component of the ERAS program.

Radical cystectomy and established outcomes following radical cystectomy

Bladder cancer is the 10th most common cancer worldwide, with 573,000 new cases and 213,000 deaths due to bladder cancer, according to the 2020 Global Cancer Observatory database [6]. According to the National Cancer Statistics, bladder cancer was the 12th most common cancer in South Korea in 2018. It affected 4,379 people (3,525 males and 854 females) and killed 1,438 (1,100 males and 338 females) [7].

Radical cystectomies are the standard treatment for non-muscle-invasive bladder cancer that has a high risk of recurrence and does not respond to muscle-invasive bladder cancer or intravesical Bacillus Calmette–Guérin therapies. Radical cystectomy is a complicated and time-consuming surgery and one of the most technically challenging surgeries performed by urologists [8]. Also, patients with bladder cancer are relatively elderly, with a median age of 73 years at diagnosis, and have various comorbidities. Even though it has been shown that using neoadjuvant chemotherapy as a standard treatment for radical cystectomy improves survival rates and is generally well tolerated, it cannot be denied that it increases physiological stress [9,10]. Large-scale studies that investigated the clinical, pathological, and oncological effects of radical cystectomy found that the pre- and postoperative mortality rate was between 0.3 and 4.5% [3,4,11]. Also, the incidence of complications within 30 days of surgery was 27% to 32%, and bowel ischemia was 4% to 18% [3-5]. The length of hospital stay was reported to be 8 to 9 days in the United States, 15 to 20 days in Europe [1], and 13 to 22 days in Korea, according to recent data from the Korean multi-institutional robotic surgery database [12]. Furthermore, after bladder resection, many patients experience physiological changes, including metabolic disorders as well as changes in body image, requiring adjustments in lifestyle, psychological, and social adaptation.

History of the ERAS Program

The ERAS program is a protocol established based on evidence to standardize the treatment of surgical patients, enhance surgical outcomes, and reduce medical costs. In the late 1990s, Kehlet first described the ERAS program to minimize surgical trauma and stress responses, reduce surgery-related complications, and accelerate pre- and postoperative recoveries [13]. In 2001, Ken Fearon and Olle Ljungqvist founded the ERAS research group to improve and standardize pre- and postoperative treatments based on evidence [4]. The ERAS Society (www.erassociety.org) has established field-specific guidelines for implementing the ERAS program based on currently available information [14]. For example, the most recent guidelines for colon resection specify 24 individual elements. The principles of ERAS in colon resection have been proven to reduce readmission rates and length of hospital stays [15-17]. Additional research is needed to confirm the role of ERAS in outcomes such as quality of life, patient satisfaction, and economic impact. However, no harmful effects of ERAS have been confirmed [18,19].

Composition of the ERAS program

The main goal of the ERAS program is to use an integrated peri-, intra-, and postoperative treatment protocol to reduce the stress response and decrease the postoperative functional impairment of targeted organs. To achieve this, the ERAS program consists of 15 to 20 individual elements.

Preoperative period

Patient education: Smoking and alcohol cessation education, nutritional assessment, and verification of colostomy or urostomy location.

Management of accompanying diseases: Management of accompanying diseases such as high blood pressure, diabetes, anemia, and nutritional supply (especially for patients with malnutrition). The management measures include: (1) fasting from fried, greasy, or meat-based foods for eight hours preoperatively; (2) fasting for six hours preoperatively from light meals and opaque beverages (e.g., tea and toast, fruit juice, milk); (3) fasting for two hours preoperatively from clear liquids (excluding alcoholic beverages, beverages containing milk, and juice); and (4) carbohydrate drinks (optional) two hours preoperatively should be considered for all patients without diabetes.

Intraoperative period

Thrombosis prevention: The preventive measures include: (1) compression stockings and low-molecular-weight heparin (which should be continued up to four weeks postoperatively for high-risk patients); (2) maintenance of normal body temperature (normothermia); (3) fluid optimization: targeted fluid therapy using an esophageal Doppler; (4) a minimally invasive surgical approach; (5) avoidance of nasogastric tube insertion: Early removal or non-insertion is recommended; and (6) no abdominal or perianal drainage: It is safe to omit drainage around the suture site or pelvic drainage (except for situations such as intestinal leakage or purulent drainage). Patients undergoing bladder resection may require a ureteral stent owing to the possibility of urinary leakage.

Postoperative period

The elements include: (1) enteral nutrition (intestinal nutrition) starting from the first day of surgery; (2) high-calorie supplements twice a day; (3) multimodal analgesia (e.g., transverse abdominis block and fast-acting opioids) for up to 48 or 72 h; (4) regular administration of opioids and nonsteroidal anti-inflammatory drugs such as acetaminophen; (5) multimodal antiemetic regimen; (6) early removal of the urinary catheter usually on the first day of surgery; and (7) analyzing outcomes after applying the ERAS program for radical cystectomy. Through the efforts of urologists who aimed to implement evidence-based ERAS programs for radical cystectomy, the ERAS Society released recommendations for radical cystectomy [20]. Many ERAS principles used in radical cystectomy are based on evidence proven in other surgical procedures (Table 1).

Preoperative ERAS elements

The key to successfully performing the ERAS protocol is smooth communication between the medical team, including patients, urologists, anesthesiologists, pain specialists, general practitioners, and specialized nurses in urinary incontinence. It is crucial to identify patients at high risk for surgery before performing a radical cystectomy. This is because it helps explain the risk-benefit ratio of surgery and predict postoperative management decisions. Particularly, evaluation for bladder cancer is essential because it primarily occurs in individuals around the age of 70. A simple self-assessment questionnaire should be used to obtain a thorough medical history and identify any pre-existing cardiovascular and respiratory diseases. A patient's functional ability can be expressed in Metabolic Equivalents (METs). One MET represents an adult's oxygen consumption (3.5 ml oxygen uptake/kg/min) at rest, while various levels of exercise can be expressed in METs. Patients

Table 1: Phases of ERAS protocol elements.

Preoperative elements	Intraoperative elements	Postoperative elements
Counseling and education · Provide leaflets or multimedia information · Set expectations · Discharge planning · Stoma education	Antibiotic prophylaxis and skin preparation	Avoid postoperative nasogastric intubation
Medical optimization · Optimize medical diseases · Encourage smoking and alcohol cessation · Physical conditioning (prehab) · Improve nutritional status	Anesthetic protocols · Use of thoracic epidural · Neural blockade · Minimal opioid use · Prevention of intraoperative hypothermia · Individualized goal-directed fluid therapy	Early enteric feeding
Avoid mechanical bowel preparation	Minimize incision (minimally invasive approach)	Early mobilization
Avoid fasting	Less bowel manipulation	Ureteral stenting
Carbohydrate loading	Minimization of blood loss and transfusion	Chewing gum
Alvimopan administration	Instillation of local anesthetic at incision sites	Multimodal opioid-sparing analgesia combined with regional or local anesthesia
Preanesthetic medication Avoid long-acting sedatives		Nausea and vomiting prophylaxis
Thromboembolic prophylaxis Low-molecular-weight or unfragmented heparin Compression stockings and intermittent pneumatic compression devices		Extended VTE prophylaxis
		Discharge planning

ERAS: Enhanced Recovery After Surgery; VTE: Venous Thromboembolism

undergoing major surgery should be able to perform at least four METs, which is about the same as being able to climb one flight of stairs without difficulty [21].

Preoperative patient consultation and education: The first step of the ERAS protocol is to consult with the patient and explain to them the purpose and prognosis of the surgery, the surgical procedure, the location of the catheter, the length of the hospital stays, and the discharge criteria. While there is no specific evidence that preoperative consultation improves the outcomes of radical cystectomy [20], providing detailed information to patients preoperatively can reduce their fears and anxieties, promote postoperative recovery, and shorten their hospital stay [22,23]. Also, there should be detailed information on managing urinary incontinence and the orthotopic neobladder as well as the method of using the catheter [24,25].

Preoperative patient assessment and management: Preoperative measures, physical activity, smoking cessation, and the control of comorbidities (such as diabetes, hypertension, and anemia) have been shown to decrease complications after radical cystectomy [26,27]. Preoperative physical activity and exercise can promote recovery [28], and preoperative malnutrition is known to increase the incidence of postoperative complications and mortality; therefore, appropriate management is necessary at least two weeks preoperatively to reduce complications [29]. Alcohol abusers have a two- to three-fold higher risk of postoperative complications, and the most common complications are bleeding, wound complications, and cardiopulmonary complications. Abstinence from alcohol for one month preoperatively can improve organ function and reduce the incidence of postoperative complications [30,31]. Smoking is another factor that negatively affects recovery. Current smokers have an increased risk of postoperative pulmonary and wound complications [32], and smoking cessation for one month is necessary to reduce the incidence of complications [32,33].

Oral mechanical bowel preparation: Traditional mechanical bowel preparation before colorectal surgery has been reported to cause dehydration, electrolyte imbalances, physiological stress, and bowel obstruction [34,35]. A meta-analysis including 5,000 patients undergoing colorectal surgery found that mechanical bowel preparation had no benefits and may be associated with anastomotic leakage and wound complications [36]. A prospective study of 30 patients receiving standard three-day mechanical bowel preparation and 32 patients not receiving mechanical bowel preparation for radical cystectomy showed no difference in the complication rate or length of hospital stay [37]. Similarly, a randomized trial of 86 patients undergoing radical cystectomy found no significant differences in the complication rate, length of hospital stays, or time to the first bowel movement between the groups receiving or not receiving mechanical bowel preparation [38]. Other randomized controlled trials also showed no difference in the recovery of bowel function, length of hospital stay, or overall complication rate between the "no bowel preparation" group (no bowel preparation *vs.* limited bowel preparation vs. enema only) and other groups [39,40].

Preoperative fasting: A Cochrane meta-analysis of 22 randomized controlled studies found that fasting from midnight until two hours preoperatively without the restriction of clear fluids did not lead to a decrease in gastric volume or increase in gastric pH compared to allowing patients to freely consume clear fluids up to two hours before anesthesia induction [41]. Based on these studies, European anesthesia guidelines allow for solids and fluids to be ingested up to two hours before anesthesia induction, with a maximum of six hours before induction [42].

Preoperative carbohydrate loading: Carbohydrate loading preoperatively involves consuming a carbohydrate-rich diet, similar to a pre-marathon meal, to accumulate glycogen as an energy source [14,43]. Preoperative carbohydrate loading has been reported to reduce thirst, maintain lean body mass and muscle strength, and aid in the early recovery of bowel function. A meta-analysis of patients undergoing laparotomies found that preoperative carbohydrate loading significantly reduced the length of hospital stay [43]. It was particularly effective in reducing insulin resistance and hyperglycemia in patients with diabetes undergoing surgery [14,43].

Preoperative alvimopan administration: Alvimopan was administered as part of the ERAS protocol preoperatively, which focuses on preventing the most common complication after radical cystectomy, which is postoperative ileus. Postoperative ileus can impair a patient's nutritional status, increase the risk of complications, and prolong the length of the hospital stay and cost [2,5,44]. Alvimopan (brand name Entereg) is a peripherally acting μ-opioid receptor antagonist that effectively blocks μ-opioid receptors in the gastrointestinal tract while avoiding central nervous system depression caused by opioid-like antagonists, as it does not cross the blood-brain barrier [45]. Alvimopan is the only Food and Drug Administration-approved product for the treatment of postoperative ileus and was approved in May 2008 [46].

Currently, a multicenter randomized controlled trial is being performed to evaluate the individual components of ERAS after radical cystectomy and examine the effects of alvimopan on the recovery of bowel function [47]. In this trial, the alvimopan cohort had a shorter length of hospital stay (7.4 *vs.* 10.1 days), a faster time to bowel movement (5.5 *vs.* 6.8 days), and 20% fewer surgery-related complications (re-interventions for bowel resection, prolonged length of the hospital stay, or postoperative ileus). Additionally, Tobis et al. reported that alvimopan administration shortened the time to recovery of bowel function (five *vs.* six days) and initiation of diet (six *vs.* seven days) in 117 patients who underwent robot-assisted radical cystectomy [48]. Hypokalemia (9.5%), dyspepsia (7.0%), urinary retention (3.3%), and delayed urination (3.2%) are the four most common side effects of alvimopan [45].

Preanesthetic medications: Preoperative anxiolytics have been reported to interfere with early postoperative dietary recovery [48]. Long-acting sedatives can increase cognitive impairment in elderly patients and may interfere with early postoperative dietary recovery [14]. The ERAS guidelines recommend the use of short-acting sedatives for postoperative recovery and advise against using long-acting sedatives [14].

Prevention of thromboembolism: The incidence of clinically significant deep vein thrombosis or thromboembolism after radical cystectomy is reported to be approximately 4% [49]. Patients who receive neoadjuvant chemotherapy before radical cystectomy have a higher risk of postoperative thromboembolism [50]. Therefore, the use of low-molecular-weight or unfractionated heparin for thromboembolic prophylaxis is recommended [51]. Additionally, compression stockings and intermittent pneumatic compression devices can reduce this risk. The ERAS guidelines recommend maintaining low-molecular-weight heparin for at least four weeks postoperatively for thromboembolic prophylaxis [14].

Intraoperative ERAS elements

The ERAS program recommends the following considerations for both anesthesia and surgery during the intraoperative period.

Prophylactic antibiotic use and skin preparation: As radical cystectomy is considered a "clean-contaminated" surgery, antibiotic prophylaxis for patients undergoing radical cystectomy should target aerobic and anaerobic bacteria. According to the European Association of Urology guidelines, antibiotics should be administered one hour preoperatively and continued for up to 24 h. An extension of up to 72 h has been recommended for patients with specific infection risks or prolonged operative periods (>3 h) [52].

In a study comparing various types of preoperative skin preparations, the overall incidence of surgical site infection was 40% lower in the chlorhexidine-alcohol group than in the povidone-iodine group [53]. Regarding optimal skin preparation, several ERAS guidelines recommend preoperative skin scrubbing with chlorhexidine and alcohol to prevent surgical site infections [20,27].

Anesthesia protocol: According to studies on ERAS for radical cystectomy and previous studies on colorectal surgery, the ERAS anesthesia protocol should include thoracic epidural analgesia (T9–T11), minimal use of narcotic analgesics, and prevention strategies for hypothermia, hypoxemia, and hypovolemia [54]. Although there have been no prospective randomized studies evaluating the use of thoracic epidural analgesia for the management of radical cystectomy, it has been proven to reduce the stress response to surgery, effectively relieve pain, decrease postoperative complications, and accelerate the recovery of bowel function in patients undergoing colorectal surgery compared to patient-controlled anesthesia [55]. Furthermore, thoracic epidural analgesia is widely recommended for a shorter hospital stay and postoperative ileus in patients undergoing colorectal surgery [27]. Recently, the ERAS Society for Cystectomy strongly recommended the use of thoracic epidural analgesia for 72 h postoperatively as an effective ERAS protocol for radical cystectomy [20].

Prevention of intraoperative hypothermia: Intraoperative hypothermia (core body temperature <36°C) commonly occurs during surgery and can induce vasoconstriction, which can promote surgical site infection [56]. This ultimately decreases tissue oxygen tension, reduces collagen deposition, weakens wound healing strength, and directly impairs immune function. Prevention of intraoperative hypothermia in patients undergoing colorectal surgery has been reported to reduce the incidence of infectious complications, protect against postoperative coagulopathy, and decrease the length of hospital stay [56,57]. Since radical cystectomy has a similar pathophysiology to hypothermia, it is strongly suggested that intraoperative hypothermia be avoided. The two most effective strategies for preventing hypothermia are the use of a forced-air warming blanket and warmed intravenous fluids [56].

Intra- and postoperative management of fluid: In patients undergoing radical cystectomies, intraoperative management of fluid can be challenging because of the inability to measure urine output. Both fluid overload and hypovolemia can lead to reduced visceral perfusion, resulting in bowel ischemia, increased morbidity, and a prolonged hospital stay [58]. Goal-Directed Fluid Therapy (GDFT), which involves adjusting fluid and pressor agent use using cardiac output monitors such as transesophageal Doppler, aims to optimize tissue perfusion and improve bowel perfusion, thereby reducing bowel ischemia and postoperative bowel obstruction [58]. GDFT has been shown to improve postoperative recovery and reduce complications and length of stay in patients undergoing colorectal surgery [58,59]. In a small randomized controlled trial of 60 patients undergoing radical cystectomy (32 in the experimental group and 34 in the control group), Pillai et al. reported that patients receiving GDFT had a reduced incidence of postoperative bowel obstruction, ileus, and vomiting at 24 and 48 h postoperatively [60].

A minimally invasive approach: In 2003, robot-assisted radical cystectomy was first reported and was reported to use smaller incisions than open surgery, as well as to reduce the use of analgesics, bowel handling, and blood loss [61,62]. According to a recent meta-analysis comparing open- and robot-assisted radical cystectomies,

robot-assisted surgery resulted in less blood loss and a shorter hospital stay [63]. However, open surgery had a shorter operative period than robot-assisted surgery.

Recently, the results of the Randomized Open versus Robotic Cystectomy Trial, a multicenter, open-label, non-inferiority phase III randomized controlled trial comparing robot-assisted and open radical cystectomies, were reported; however, no significant differences were found in the overall and major complication rates between the two surgeries [64].

Management of surgical drains: Traditionally, surgical drains have been used postoperatively at the incision site to monitor problems like infection and urinary leakage. However, the ERAS protocol recommends removing the drain as soon as possible postoperatively [65]. A meta-analysis of colorectal surgery reported that intra-abdominal drainage did not provide any benefits in terms of anastomotic leakage, wound infection, re-surgery, extracolonic complications, or mortality [66]. In the case of radical cystectomy, urinary leakage can affect bowel recovery; however, recent studies have recommended removing the drain on the first day of surgery if there is no evidence of urinary leakage in robot-assisted radical cystectomy [67].

Postoperative ERAS elements

Traditionally, patients undergoing radical cystectomies typically undergo prolonged fasting and a long hospital stay and use a nasogastric tube until passing gas. However, according to ERAS, new postoperative treatment standards are recommended, considering various factors.

Urinary drainage: The placement of a ureteral stent is associated with an improvement in urine leakage, a reduction in postoperative ureteral-intestinal stricture and bowel obstruction, and a reduction in metabolic acidosis [65]. The optimal duration of postoperative ureteral stent placement is unknown. However, according to studies, the ureteral stent can be removed within two weeks of ileal conduit surgery, and 70% of respondents for orthotopic neobladder removal reported removing the ureteral stent within two weeks of surgery, whereas the remaining 30% reported removal after two weeks [67]. The ERAS guidelines recommend removing the urinary catheter on the first day of surgery and the ureteral stent five days postoperatively, but the evidence is unclear [14].

Nasogastric intubation: Early removal of nasogastric intubation is an important element of ERAS protocols. In a meta-analysis of 33 randomized controlled trials, which included 5,240 patients who underwent abdominal surgery with or without intraoperative nasogastric intubation or had early removal of the nasogastric tube postoperatively, patients showed early recovery of bowel function ($p<0.00001$) and decreased pulmonary complications ($p=0.01$) compared to patients who were retained with nasogastric intubation following the standard approach (intraoperative nasogastric intubation, confirmation of postoperative recovery of bowel function, and removal of the nasogastric tube) [68]. Early removal of nasogastric intubation in the urologic field was first introduced by Pruthi et al. [69] for patients undergoing radical cystectomy. The study found that patients had improved postoperative outcomes, including lower rates of complications and early recovery, after removing the nasogastric tube on the first day of surgery and administering clear fluids on the second day, followed by a regular diet starting on the fourth day.

Prevention of postoperative bowel obstruction: One of the most common complications of radical cystectomy is postoperative bowel obstruction, which is also one of the major causes of delayed hospital discharge. It can cause an imbalance in the patient's nutritional status, increase morbidity, and prolong the hospital stay [5,44]. Specific treatments related to the prevention of postoperative bowel obstruction, like preoperative alvimopan administration, appropriate management of fluid, minimally invasive surgery, and ureteral stent placement, have been described in other elements of ERAS. Also, a mixture of ondansetron and dexamethasone has been reported to prevent nausea and vomiting following surgery and postoperative bowel obstruction [70,71]. Randomized controlled trials, including a study of 32 patients undergoing open radical cystectomy (17 who did not chew gum and 15 who did), a study of 28 patients undergoing robotic radical cystectomy (13 who did not chew gum and 15 who did), and a meta-analysis of 272 gastrointestinal surgeries, reported that chewing gum can help prevent postoperative bowel obstruction and shorten the time to the first bowel movement [72,73]. A randomized controlled trial with 200 patients having colorectal surgery (bisacodyl *vs.* placebo) found that prophylactic oral laxatives (bisacodyl) can help the recovery of normal bowel function quickly and shorten the time until the first bowel movement [74]. Robotic radical cystectomy has been reported to promote faster recovery of bowel function than open radical cystectomy [61].

Early nutrition: Contrary to the conventional surgical belief that a diet should only be started after the recovery of intestinal function, starting the diet early can reduce insulin resistance and provide beneficial effects on muscle function, wound healing, and sepsis [75]. There is no clear evidence for the benefits of early nutrition in radical cystectomy, but Behrns et al. reported that starting with clear fluids on the second day of bowel surgery and progressing rapidly to a regular diet could shorten the length of hospital stay without increasing the postoperative complication rate [76]. In a meta-analysis of 15 randomized clinical trials on 1,240 gastrointestinal surgeries, the early nutrition group showed a decrease in overall complications compared to the traditional diet group and did not show negative effects on mortality, pneumonia, anastomotic leakage, bowel recovery time, or length of hospital stay [77]. So, even in patients undergoing radical cystectomy, early nutrition is recommended despite insufficient evidence, considering the evidence presented and the incidence of malnutrition in surgical patients. However, postoperative early nutrition can increase vomiting; therefore, active interventions such as periodic antiemetics, chewing gum, cholinergic stimulants, laxatives, prokinetic agents, and limited use of anesthetics are recommended. Additionally, minimizing postoperative intravenous fluid administration is important to prevent fluid overload and intestinal edema [78].

Postoperative pain control: Effective pain control with minimal narcotic side effects is a key component of ERAS, which combines partial or local anesthesia with various methods of pain control. The ERAS guidelines recommend thoracic epidural analgesia for at least 72 h instead of systemic opioid analgesics for the management of pain [14]. In colorectal surgery, thoracic epidural analgesia has been shown to reduce pain, intestinal obstruction, and flatulence and promote postoperative recovery [29].

Early mobilization: The use of appropriate pain medications enables early postoperative mobilization, reduces insulin resistance, decreases the occurrence of thromboembolism and pneumonia, increases muscle strength, reduces bowel obstruction, and shortens the hospital stay [27,79,80]. Jensen et al. found that early mobilization

after a radical cystectomy enhances a patient's ability to perform daily activities [28]. Early mobilization is widely established and implemented in ERAS protocols for radical cystectomy.

Discharge criteria: The ERAS protocol recommends discharge when the patient has effective self-management of pain, appropriate nutrition intake, recovery of normal bowel function, and no other clinical or biochemical problems, including urinary diversion or continent cutaneous reservoir function [57]. Additionally, patients should receive sufficient education on the management of urinary diversion, such as changing the urinary diversion bag and managing continent cutaneous reservoirs.

Quality of life: Several researchers have evaluated the impact of the ERAS protocol on quality of life [81,82]. Stowers et al. [81] reported no improvement in the quality of life between ERAS and standard care for various abdominal surgeries, excluding radical cystectomies. Karl et al. [82] randomly assigned patients who underwent radical cystectomy to receive conventional or ERAS protocol treatments and evaluated the results using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-30. They reported an improvement in the continuous emotional functioning score in the ERAS group. This study is the first to demonstrate the emotional benefits of applying the ERAS protocol in patients undergoing radical cystectomy.

Future Direction

The ERAS protocol is continually evolving through a multidisciplinary approach to the care of complex surgical patients. The management of pre- and postoperative care is important at each stage and is interconnected. Particularly, smooth communication among all participants involved in a patient's treatment is crucial, especially at various stages that require multiple interventions such as the management of fluid and pain.

Preoperative care

Currently, almost all patients undergo the same preoperative elements of the ERAS protocol. However, individual patient factors, including age, social support systems, financial factors, and comorbidities, can stratify the risk and modify the ERAS protocol to provide more beneficial treatment to each patient. Additionally, concepts such as prehabilitation and nutritional interventions to optimize a patient's preoperative medical and functional status are continuously being studied. In the case of radical cystectomy, which requires urgent surgical intervention, the time to improve a patient's health or functional status is considerably limited. Nevertheless, attempts to improve patient outcomes in less invasive ways preoperatively are being pursued [83]. Future research will continue to provide additional methods to optimize pre- and postoperative care to improve clinical outcomes [84].

Intraoperative care

The most significant recent change in radical cystectomy is the introduction of robotic surgery. In a randomized controlled trial comparing open and robotic-assisted radical cystectomies, robotic bladder resection showed an increase in surgical time and a decrease in blood loss compared to open surgery. However, there was no significant difference in the length of hospital stay, complication rate, or quality of life outcomes between the two groups [52]. More research will show if robotic bladder resection is effective against cancer and if it has other potential benefits, such as its functional efficacy. However, current results suggest that the application of the ERAS protocol has a greater impact on clinical outcomes than the surgical approach, and the European Association of Urology Robotic Urology's Section Scientific Working Group recommends the use of the ERAS protocol for pre- and post-operative care in robotic-assisted radical cystectomy [53].

With increased awareness of the importance of intraoperative management of fluids and the emphasis on the multidisciplinary nature of ERAS, the role of anesthesiologists and physicians in improving patient care and outcomes has been highlighted. Optimization of the management of fluids through GDFT is essential for the use of fluids and blood products. Several studies have reported an increased risk of cancer-related mortality and recurrence in patients receiving intraoperative transfusions [85,86]. Wuethrich et al. [87] reported the results of a prospective study on continuous noradrenaline infusion and restricted fluid supply during cystectomy. The use of this restricted fluid supply protocol resulted in significantly lower blood loss and transfusion rates than the standard protocol, and subsequent studies using this protocol reported a decrease in gastrointestinal complications and bleeding rates [69,88]. Anesthesiologists and physicians are developing optimal methods for monitoring patient status and managing pain through epidural anesthesia, local blockade, and optimal management of fluid intraoperatively.

Postoperative period

One of the most evident areas in need of additional research and improvement is the determination of methods to prevent infectious complications and optimize pain control. Infectious complications are one of the most common reasons for readmission after radical cystectomy [89]. While prophylactic antibiotic administration before surgical incision is recommended for the majority of surgeries, the optimal range of antibiotic use before and after radical cystectomies is not well established. Particularly, additional research is needed regarding the scope and duration of prophylactic antibiotic use beyond 24 h postoperatively. Various factors, including postoperative rehabilitation programs and optimal nutrition, may be clinically important in improving treatment outcomes for patients undergoing radical cystectomy and will be integrated into ERAS in the future [90].

Conclusion

ERAS has firmly established itself as an essential component of perioperative care for patients undergoing a radical cystectomy, and studies have shown that it helps patients recover faster postoperatively. However, additional research is needed to determine the specific elements of ERAS that have the most practical impact on the clinical course of patients undergoing radical cystectomy. It should also be noted that the evidence supporting specific items in the ERAS guidelines for radical cystectomy is based on the results of colorectal surgery rather than radical cystectomy. High-level prospective randomized controlled trials on patients who are undergoing a radical cystectomy are required to identify the best ways to improve the treatment pathway for patients.

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References

1. Cha EK, Sfakianos JP, Sukhu R, Yee AM, Sjoberg DD, Bochner BH. Poor prognosis of bladder cancer patients with occult lymph node metastases treated with neoadjuvant chemotherapy. BJU Int. 2018;122:627-32.
2. Shabsigh A, Korets R, Vora KC, Brooks CM, Cronin AM, Savage C, et al. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. Eur Urol. 2009;55:164-74.
3. Novotny V, Hakenberg OW, Wiessner D, Heberling U, Litz RJ, Oehlschlaeger S, et al. Perioperative complications of radical cystectomy in a contemporary series. Eur Urol. 2007;51:397-401; discussion 401-2.
4. Johnson SC, Smith ZL, Golan S, Rodriguez 3rd JF, Smith ND, Steinberg GD, et al. Temporal trends in perioperative morbidity for radical cystectomy using the National Surgical Quality Improvement Program database. Urol Oncol. 2017;35:659.e13-.e19.
5. Chang SS, Cookson MS, Baumgartner RG, Wells N, Smith Jr JA. Analysis of early complications after radical cystectomy: Results of a collaborative care pathway. J Urol. 2002;167:2012-6.
6. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209-49.
7. Hong S, Won YJ, Park YR, Jung KW, Kong HJ, Lee ES, et al. Cancer Statistics in Korea: Incidence, mortality, survival, and prevalence in 2017. Cancer Res Treat. 2020;52:335-50.
8. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder cancer incidence and mortality: A global overview and recent trends. Eur Urol. 2017;71:96-108.
9. Nicholson A, Lowe MC, Parker J, Lewis SR, Alderson P, Smith AF. Systematic review and meta-analysis of enhanced recovery programmes in surgical patients. Br J Surg. 2014;101:172-88.
10. Network NCC. Bladder Cancer (Version: 4.2021). Editors". City.
11. Xiao J, Wang M, He W, Wang J, Yang F, Ma XY, et al. Does postoperative rehabilitation for radical cystectomy call for enhanced recovery after surgery? A systematic review and meta-analysis. Curr Med Sci. 2019;39:99-110.
12. Oh JJ, Lee S, Ku JH, Kwon TG, Kim TH, Jeon SH, et al. Oncological outcome according to attainment of pentafecta after robot-assisted radical cystectomy in patients with bladder cancer included in the multicentre KORARC database. BJU Int. 2021;127:182-9.
13. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth. 1997;78:606-17.
14. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for perioperative care in elective colorectal surgery: Enhanced Recovery After Surgery (ERAS®) society recommendations: 2018. World J Surg. 2019;43:659-95.
15. Varadhan KK, Neal KR, Dejong CHC, Fearon KCH, Ljungqvist O, Lobo DN. The Enhanced Recovery After Surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: A meta-analysis of randomized controlled trials. Clin Nutr. 2010;29:434-40.
16. Spanjersberg WR, Reurings J, Keus F, van Laarhoven CJ. Fast track surgery versus conventional recovery strategies for colorectal surgery. Cochrane Database Syst Rev. 2011;(2):Cd007635.
17. Adamina M, Kehlet H, Tomlinson GA, Senagore AJ, Delaney CP. Enhanced recovery pathways optimize health outcomes and resource utilization: A meta-analysis of randomized controlled trials in colorectal surgery. Surgery. 2011;149:830-40.
18. Sammour T, Zargar-Shoshtari K, Bhat A, Kahokehr A, Hill AG. A programme of Enhanced Recovery After Surgery (ERAS) is a cost-effective intervention in elective colonic surgery. N Z Med J. 2010;123:61-70.
19. Khan S, Wilson T, Ahmed J, Owais A, MacFie J. Quality of life and patient satisfaction with enhanced recovery protocols. Colorectal Dis. 2010;12:1175-82.
20. Cerantola Y, Valerio M, Persson B, Jichlinski P, Ljungqvist O, Hubner M, et al. Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS®) society recommendations. Clin Nutr. 2013;32:879-87.
21. Frith C, Wakelam J, Vasdev N, Boustead G, Adshead JM, Lan T, et al. The role of an enhanced recovery protocol in patients undergoing robotic radical cystectomy. Urology. 2014.
22. Kiecolt-Glaser JK, Page GG, Marucha PT, MacCallum RC, Glaser R. Psychological influences on surgical recovery. Perspectives from psychoneuroimmunology. Am Psychol. 1998;53:1209-18.
23. Egbert LD, Battit GE, Welch CE, Bartlett MK. Reduction of postoperative pain by encouragement and instruction of patients. A study of doctor-patient rapport. N Engl J Med. 1964;270:825-7.
24. Merandy K, Morgan MA, Lee R, Scherr DS. Improving self-efficacy and self-care in adult patients with a urinary diversion: A pilot study. Oncol Nurs Forum. 2017;44:E90-e100.
25. Ali NS, Khalil HZ. Effect of psychoeducational intervention on anxiety among Egyptian bladder cancer patients. Cancer Nurs. 1989;12:236-42.
26. Hollenbeck BK, Miller DC, Taub D, Dunn RL, Khuri SF, Henderson WG, et al. Identifying risk factors for potentially avoidable complications following radical cystectomy. J Urol. 2005;174:1231-7; discussion 1237.
27. Nygren J, Thacker J, Carli F, Fearon KCH, Norderval S, Lobo DN, et al. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. World J Surg. 2013;37:285-305.
28. Jensen BT, Petersen AK, Jensen JB, Laustsen S, Borre M. Efficacy of a multiprofessional rehabilitation programme in radical cystectomy pathways: A prospective randomized controlled trial. Scand J Urol. 2015;49:133-41.
29. Gregg JR, Cookson MS, Phillips S, Salem S, Chang SS, Clark PE, et al. Effect of preoperative nutritional deficiency on mortality after radical cystectomy for bladder cancer. J Urol. 2011;185:90-6.
30. Tonnesen H, Kehlet H. Preoperative alcoholism and postoperative morbidity. Br J Surg. 1999;86:869-74.
31. Tonnesen H, Rosenberg J, Nielsen HJ, Rasmussen V, Hauge C, Pedersen IK, et al. Effect of preoperative abstinence on poor postoperative outcome in alcohol misusers: Randomised controlled trial. BMJ. 1999;318:1311-6.
32. Sorensen LT, Karlsmark T, Gottrup F. Abstinence from smoking reduces incisional wound infection: A randomized controlled trial. Ann Surg. 2003;238:1-5.
33. Lindström D, Azodi OS, Wladis A, Tønnesen H, Linder S, Nåsell H, et al. Effects of a perioperative smoking cessation intervention on postoperative complications: A randomized trial. Ann Surg. 2008;248:739-45.
34. Jung B, Matthiessen P, Smedh K, Nilsson E, Ransjö U, Påhlman L. Mechanical bowel preparation does not affect the intramucosal bacterial colony count. Int J Colorectal Dis. 2010;25:439-42.
35. Güenaga KF, Matos D, Wille-Jørgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev. 2011;2011:Cd001544.
36. Bertrand J, Siegler N, Murez T, Poinas G, Segui B, Ayuso D, et al. Impact of preoperative immunonutrition on morbidity following cystectomy for bladder cancer: A case-control pilot study. World J Urol 2014;32:233-7.
37. Tabibi A, Simforoosh N, Basiri A, Ezzatnejad M, Abdi H, Farrokhi F.

Bowel preparation versus no preparation before ileal urinary diversion. Urology. 2007;70:654-8.

38. Xu R, Zhao X, Zhong Z, Zhang L. No advantage is gained by preoperative bowel preparation in radical cystectomy and ileal conduit: A randomized controlled trial of 86 patients. Int Urol Nephrol. 2010;42:947-50.

39. Raynor MC, Lavien G, Nielsen M, Wallen EM, Pruthi RS. Elimination of preoperative mechanical bowel preparation in patients undergoing cystectomy and urinary diversion. Urol Oncol. 2013;31:32-5.

40. Aslan G, Baltaci S, Akdogan B, Kuyumcuoğlu U, Kaplan M, Cal C, et al. A prospective randomized multicenter study of Turkish Society of Urooncology comparing two different mechanical bowel preparation methods for radical cystectomy. Urol Oncol. 2013;31:664-70.

41. Brady M, Kinn S, Stuart P. Preoperative fasting for adults to prevent perioperative complications. Cochrane Database Syst Rev. 2003;(4):CD004423.

42. Smith I, Kranke P, Murat I, Smith A, O'Sullivan G, Søreide E, et al. Perioperative fasting in adults and children: Guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol. 2011;28:556-69.

43. Bilku DK, Dennison AR, Hall TC, Metcalfe MS, Garcea G. Role of preoperative carbohydrate loading: A systematic review. Ann R Coll Surg Engl. 2014;96:15-22.

44. Correia MI, da Silva RG. The impact of early nutrition on metabolic response and postoperative ileus. Curr Opin Clin Nutr Metab Care. 2004;7:577-83.

45. Neary P, Delaney CP. Alvimopan. Expert Opin Investig Drugs. 2005;14:479-88.

46. Sharma A, Jamal MM. Opioid induced bowel disease: A twenty-first century physicians' dilemma. Considering pathophysiology and treatment strategies. Curr Gastroenterol Rep. 2013;15:334.

47. Lee CT, Chang SS, Kamat AM, Amiel G, Beard TL, Fergany A, et al. Alvimopan accelerates gastrointestinal recovery after radical cystectomy: A multicenter randomized placebo-controlled trial. Eur Urol. 2014;66:265-72.

48. Tobis S, Heinlen JE, Ruel N, Lau C, Kawachi M, Wilson T, et al. Effect of alvimopan on return of bowel function after robot-assisted radical cystectomy. J Laparoendosc Adv Surg Tech A. 2014;24:693-7.

49. Tyson MD, Castle EP, Humphreys MR, Andrews PE. Venous thromboembolism after urological surgery. J Urol. 2014;192:793-7.

50. Alberts BD, Woldu SL, Weinberg AC, Danzig MR, Korets R, Badani KK. Venous thromboembolism after major urologic oncology surgery: A focus on the incidence and timing of thromboembolic events after 27,455 operations. Urology. 2014;84:799-806.

51. Ziegelmueller BK, Jokisch JF, Buchner A, Grimm T, Kretschmer A, Schulz GB, et al. Long-term follow-up and oncological outcome of patients undergoing radical cystectomy for bladder cancer following an Enhanced Recovery after Surgery (ERAS) Protocol: Results of a large randomized, prospective, single-center study. Urol Int. 2020;104:55-61.

52. Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: An advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis. 2004;38:1706-15.

53. Darouiche RO, Wall Jr MJ, Itani KMF, Otterson MF, Webb AL, Carrick MM, et al. Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis. N Engl J Med. 2010;362:18-26.

54. Tan WS, Tan MY, Lamb BW, Sridhar A, Mohammed A, Baker H, et al. Intracorporeal robot-assisted radical cystectomy, together with an enhanced recovery programme, improves postoperative outcomes by aggregating marginal gains. BJU Int. 2018;121:632-9.

55. Carli F, Kehlet H, Baldini G, Steel A, McRae K, Slinger P, et al. Evidence basis for regional anesthesia in multidisciplinary fast-track surgical care pathways. Reg Anesth Pain Med. 2011;36:63-72.

56. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. N Engl J Med. 1996;334:1209-15.

57. Azhar RA, Bochner B, Catto J, Goh AC, Kelly J, Patel HD, et al. Enhanced recovery after urological surgery: A contemporary systematic review of outcomes, key elements, and research needs. Eur Urol. 2016;70:176-87.

58. Giglio MT, Marucci M, Testini M, Brienza N. Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: A meta-analysis of randomized controlled trials. Br J Anaesth. 2009;103:637-46.

59. Wakeling HG, McFall MR, Jenkins CS, Woods WGA, Miles WFA, Barclay GR, et al. Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. Br J Anaesth. 2005;95:634-42.

60. Pillai P, McEleavy I, Gaughan M, Snowden C, Nesbitt I, Durkan G, et al. A double-blind randomized controlled clinical trial to assess the effect of Doppler optimized intraoperative fluid management on outcome following radical cystectomy. J Urol. 2011;186:2201-6.

61. Nix J, Smith A, Kurpad R, Nielsen ME, Wallen EM, Pruthi RS. Prospective randomized controlled trial of robotic versus open radical cystectomy for bladder cancer: Perioperative and pathologic results. Eur Urol. 2010;57:196-201.

62. Menon M, Hemal AK, Tewari A, Shrivastava A, Shoma AM, El-Tabey NA, et al. Nerve-sparing robot-assisted radical cystoprostatectomy and urinary diversion. BJU Int. 2003;92:232-6.

63. Tang K, Xia D, Li H, Guan W, Guo X, Hu Z, et al. Robotic *vs.* open radical cystectomy in bladder cancer: A systematic review and meta-analysis. Eur J Surg Oncol. 2014;40:1399-411.

64. Parekh DJ, Reis IM, Castle EP, Gonzalgo ML, Woods ME, Svatek RS, et al. Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): An open-label, randomised, phase 3, non-inferiority trial. Lancet. 2018;391:2525-36.

65. Mattei A, Birkhaeuser FD, Baermann C, Warncke SH, Studer UE. To stent or not to stent perioperatively the ureteroileal anastomosis of ileal orthotopic bladder substitutes and ileal conduits? Results of a prospective randomized trial. J Urol. 2008;179:582-6.

66. Karliczek A, Jesus EC, Matos D, Castro AA, Atallah AN, Wiggers T. Drainage or nondrainage in elective colorectal anastomosis: A systematic review and meta-analysis. Colorectal Dis. 2006;8:259-65.

67. Collins JW, Patel H, Adding C, Annerstedt M, Dasgupta P, Khan SM, et al. Enhanced recovery after robot-assisted radical cystectomy: EAU robotic urology section scientific working group consensus view. Eur Urol. 2016;70:649-60.

68. Nelson R, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. Cochrane Database Syst Rev. 2007;2007:Cd004929.

69. Pruthi RS, Chun J, Richman M. Reducing time to oral diet and hospital discharge in patients undergoing radical cystectomy using a perioperative care plan. Urology. 2003;62:661-5; discussion 665-6.

70. López-Olaondo L, Carrascosa F, Pueyo FJ, Monedero P, Busto N, Sáez A. Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting. Br J Anaesth. 1996;76:835-40.

71. Biswas BN, Rudra A, Mandal SK. Comparison of ondansetron, dexamethasone, ondansetron plus dexamethasone and placebo in the prevention of nausea and vomiting after laparoscopic tubal ligation. J Indian Med Assoc. 2003;101:638, 40, 42.

72. Choi H, Kang SH, Yoon DK, Kang SG, Ko HY, Moon DG, et al. Chewing gum has a stimulatory effect on bowel motility in patients after open or robotic radical cystectomy for bladder cancer: A prospective randomized

comparative study. Urology. 2011;77:884-90.

73. Fitzgerald JE, Ahmed I. Systematic review and meta-analysis of chewing-gum therapy in the reduction of postoperative paralytic ileus following gastrointestinal surgery. World J Surg. 2009;33:2557-66.

74. Zingg U, Miskovic D, Pasternak I, Meyer P, Hamel CT, Metzger U. Effect of bisacodyl on postoperative bowel motility in elective colorectal surgery: A prospective, randomized trial. Int J Colorectal Dis. 2008;23:1175-83.

75. Schroeder D, Gillanders L, Mahr K, Hill GL. Effects of immediate postoperative enteral nutrition on body composition, muscle function, and wound healing. JPEN J Parenter Enteral Nutr. 1991;15:376-83.

76. Behrns KE, Kircher AP, Galanko JA, Brownstein MR, Koruda MJ. Prospective randomized trial of early initiation and hospital discharge on a liquid diet following elective intestinal surgery. J Gastrointest Surg. 2000;4:217-21.

77. Osland E, Yunus RM, Khan S, Memon MA. Early versus traditional postoperative feeding in patients undergoing resectional gastrointestinal surgery: A meta-analysis. JPEN J Parenter Enteral Nutr. 2011;35:473-87.

78. Smith J, Pruthi RS, McGrath J. Enhanced recovery programmes for patients undergoing radical cystectomy. Nat Rev Urol. 2014;11:437-44.

79. Patel HR, Cerantola Y, Valerio M, Persson B, Jichlinski P, Ljungqvist O, et al. Enhanced recovery after surgery: are we ready, and can we afford not to implement these pathways for patients undergoing radical cystectomy? Eur Urol. 2014;65:263-6.

80. Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: A randomized clinical trial (LAFA-study). Ann Surg. 2011;254:868-75.

81. Stowers MD, Lemanu DP, Hill AG. Health economics in enhanced recovery after surgery programs. Can J Anaesth. 2015;62:219-30.

82. Karl A, Buchner A, Becker A, Staehler M, Seitz M, Khoder W, et al. A new concept for early recovery after surgery for patients undergoing radical cystectomy for bladder cancer: results of a prospective randomized study. J Urol. 2014;191:335-40.

83. Dutton TJ, Daugherty MO, Mason RG, McGrathJS, et al. Implementation of the Exeter enhanced recovery programme for patients undergoing radical cystectomy. BJU Int. 2014;113:719-25.

84. Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Moigne-Amrani AL, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med. 2002;346:975-80.

85. Rocos B, Donaldson LJ. Alcohol skin preparation causes surgical fires. Ann R Coll Surg Engl. 2012;94:87-9.

86. Mir MC, Zargar H, Bolton DM, Murphy DG, Lawrentschuk N. Enhanced Recovery After Surgery protocols for radical cystectomy surgery: Review of current evidence and local protocols. ANZ J Surg. 2015;85:514-20.

87. Maffezzini M, Campodonico F, Canepa G, Gerbi G, Parodi D. Current perioperative management of radical cystectomy with intestinal urinary reconstruction for muscle-invasive bladder cancer and reduction of the incidence of postoperative ileus. Surg Oncol. 2008;17:41-8.

88. Daneshmand S, Ahmadi H, Schuckman AK, Mitra AP, Cai J, Miranda G, et al. Enhanced recovery protocol after radical cystectomy for bladder cancer. J Urol. 2014;192:50-5.

89. Danna BJ, Wood EL, Kukreja JEB, Shah JB. The future of enhanced recovery for radical cystectomy: Current evidence, barriers to adoption, and the next steps. Urology. 2016;96:62-8.

90. Hamilton-Reeves J, Holzbeierlein JM, Unger JM, Lew DL, Fisch MJ, Henry NL. A randomized phase III double-blind clinical trial (S1600) evaluating the effect of immune-enhancing nutrition on radical cystectomy outcomes. J Clin Oncol. 2018;36:TPS529-TPS.