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Gastrointestinal Complications in Patients Who Undergo Radical Cystectomy with Enhanced Recovery Protocol

Hooman Djaladat[1] · **Siamak Daneshmand**[1]

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Abstract Gastrointestinal (GI) complications are among the most common complications following radical cystectomy and urinary diversion. The most common is postoperative ileus, although its precise pathophysiology is not completely understood. Enhanced recovery after surgery (ERAS) protocols include evidence-based steps to optimize postoperative recovery and shorten hospital stay, mainly through expedited GI function recovery. They include avoiding bowel preparation and postoperative nasogastric tube, early feeding, non-narcotic pain management, and the use of cholinergic and mu-receptor opioid antagonists. We reviewed the literature in regard to GI complications using enhanced recovery protocols and share our institutional experience with over 300 patients.

Keywords Cystectomy · Bladder cancer · Enhanced recovery · Complications · Gastrointestinal

Introduction

Bladder cancer is the fourth and eighth most common cancers in men and women, respectively, in the USA [1]. Radical cystectomy (RC) remains the gold standard treatment for muscle-invasive and high-risk non-invasive urothelial bladder carcinoma. It is among the most morbid operations in urology with high rates of complications; up to 80 % in some series [2•, 3, 4]. There has been lack of standard reporting of complications after RC until Shabsigh et al. defined a reporting methodology for post-cystectomy complications [3]. The reported 90-day complication rate after RC in this series was 64 %, though 51 % had minor complications.

The vast majority of patients will have some degree of GI dysfunction/motility disorder following RC; however, 17–30 % will experience more severe GI-related complications early postoperatively [3, 5–7]. Contributing factors include general anesthesia, bowel manipulation, and isolation for use in urinary diversion as well as uncommon complications such as bowel or urine leak. Expected GI dysfunction after RC includes mild nausea, anorexia, and weight loss that should not be considered complications of surgery. Minor complications include persistent nausea, vomiting, postoperative ileus (POI), need for nasogastric tube (NGT) and partial bowel obstruction (PBO), need for total parenteral nutrition (TPN), and non-infectious or infectious diarrhea (enterocolitis). Major complications include complete bowel obstruction, GI bleeding, bowel leak, and enteric fistulas [3, 5, 8, 9•].

Enhanced recovery after surgery (ERAS) protocols were originally introduced in colorectal surgery and have been associated with lower rates of GI complications as well as shorter hospital stay [10–12]. Similar protocols have been used in patients undergoing RC. Our group and others have demonstrated evidence-based perioperative pathways that can improve postoperative recovery and shorten length of stay (LOS) without increasing re-admission rates [2•, 5]. Several studies have investigated early postoperative complications after application of enhanced recovery protocol in RC patients; however, few have focused on GI-specific complications in prospective fashion. Given that GI complications are among the most common morbidities after RC, it is

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✉ Siamak Daneshmand
daneshma@med.usc.edu

[1] Institute of Urology, Norris Comprehensive Cancer Center, University of Southern California, 1441 Eastlake Avenue, Suite 7416, 90089 Los Angeles, CA, USA

worthwhile to review the current literature and report recent advances at reducing these complications.

GI Complications Following RC with Enhanced Recovery Protocol

(a) Postoperative ileus

The most common GI complication after RC is postoperative ileus (POI), which is sometimes considered to be equivalent to partial bowel obstruction (PBO) [2•, 3, 5, 6, 8], though the mechanisms are quite different. Transient slowing of bowel motility after major abdominal surgery is expected for the first 24–48 h [8]. Although there is no standard definition of POI, it is generally defined as oral intake intolerance that persists beyond 5 days after surgery or by nausea and vomiting accompanied by abdominal distention that requires GI rest with or without a nasogastric tube (NGT) [3, 8]. POI accounts for the majority of extended hospital stays after RC and the attendant increases in financial cost [8]. The pathophysiology of POI is complex and not completely understood. General anesthesia and opiates in particular have shown to affect bowel motility [13]. Surgical trauma and bowel manipulation may also induce a sympathetic response that can decrease bowel peristaltic activity [14]. Exposure of bowel to urine may also induce an inflammatory response that can be associated with ileus. Although most traditional studies have reported the incidence of POI up to 25 % after RC, recent enhanced recovery protocols have shown improved results. ERAS pathways implement evidence-based steps that are mostly focused on hastening GI recovery. The components of enhanced recovery protocol that have been shown to impact earlier GI recovery are avoiding bowel preparation and postoperative NGT, less narcotic use, and implementation of a μ-receptor antagonist (alvimopan) [2•, 15–18]. Adamakis et al. showed in a randomized trial that early NGT removal decreases time to bowel transit, morbidity, and LOS [19]. A Memorial Sloan Kettering study showed that early NGT removal and prokinetic agents are associated with less GI and pulmonary complications [20]. Prolonged NGT and bowel preparation has been shown to increase risk of POI and prolong LOS [8, 21]. Chewing gum has also been shown in multiple trials to be associated with reduced time to bowel function, lower rate of POI, and shortened LOS [5, 8, 10, 22], although its use in modern ERAS protocols that implement early feeding is unclear. Early feeding has been shown to provide better nutritional status and overcome early negative nitrogen balance [7]. In the colorectal population, early feeding has been compared to historical delayed feeding with no difference in risk of leak/dehiscence [23]. Randomized studies have shown resuming a diet early after abdominal surgery is safe, associated with less morbidity and earlier discharge [24]; however, there is no study in RC population on the effect of early feeding and GI complications. Early feeding and normal diet should be encouraged as soon as possible after RC as there is no evidence supporting prolonged fasting postoperatively [19]. In addition, a recent nutritional trial by Hamilton-Reeves et al. showed a 15 % reduction in postoperative complications with specialized immunonutrition (SIM) compared to a matched control before and after RC [25•]. Additional trials are underway to investigate whether specific nutrition support can further decrease morbidity after RC. Meticulous intraoperative fluid management may also contribute to a decrease in POI. Pillai et al. examined perioperative fluid management (through trans-esophageal echocardiographic doppler study) in an RCT fashion and showed that optimization of perioperative fluid intake is associated with decreased time to bowel function and other morbidities [26]. We have also observed an increased complication rate with increased intraoperative fluid intake. In an analysis of 180 patients within our ERAS cohort, multivariable logistic regression demonstrated a significant independent association between total intraoperative fluid intake and 90-day complications (OR = 1.41 for each 1000 cc fluid, 95 % CI 1.05–1.95, $p = 0.04$) after controlling for age, BMI, and CCI (unpublished data). Despite all efforts to minimize intraoperative fluid intake and avoiding excess fluid transfer, there is still no standard protocol for efficient intraoperative and early postoperative fluid management. We recommend avoidance of fluid overload perioperatively with liberal use diuretics as needed. There is now great interest within various ERAS protocols in implementing a perioperative goal-directed fluid therapy protocol that relies on cardiac stroke volume optimization to maintain optimal intraoperative and early postoperative fluid volumes and hence improve clinical outcomes.

Alvimopan has probably been the most significant advancement in the last 5–10 years in decreasing POI. Multiple double blind randomized studies have proven the efficacy of alvimopan to hasten GI recovery in major abdominal surgeries. Wolff et al. performed a randomized controlled trial (RCT) in 510 patients and showed that 12 mg alvimopan can significantly decrease POI and accelerate time to discharge [27]. Similar results were achieved by Viscusi et al. who examined 666 patients (three arms; placebo, 6 mg, and 12 mg alvimopan) and showed significantly faster bowel recovery with 12 mg alvimopan [28]. A multicenter randomized placebo-controlled trial of alvimopan in RC patients revealed that cases experienced quicker recovery (5.5 vs. 6.8 days; HR 1.8; $p < 0.0001$), shorter mean LOS (7.4 vs. 10.1 days; $p = 0.005$), and fewer episodes of POI (8.4 vs. 29 %; $p < 0.001$) [29•]. Alvimopan was concluded to be an integral part of ERAS by accelerating GI recovery and shortening LOS. To date, there is no standard enhanced recovery pathway and each protocol has implemented some of these steps.

Maffezzini et al. [7] applied an enhanced recovery pathway to a cohort of 107 patients to determine if specific elements would reduce GI complications. Their pathway included lack

of mechanical bowel preparation or postoperative NGT, avoidance of hypovolemia and hypothermia intraoperatively, and early postoperative feeding. They used parenteral and enteral (via a jejunal cannula) nutrition to help decrease POI. They showed that decreased median time to bowel function and tolerance of regular diet could be achieved with their care pathway. In their study, the incidence of POI was 17.7 %. Chang and colleagues also examined the effects of an enhanced recovery pathway in RC patients including a standardized operative approach with preoperative bowel preparation but no postoperative NGT [30]. POI incidence in this study was 17 %. They concluded that complication rates were comparatively favorable with other cohorts using such pathway. Pruthi et al. described a fast-track program to optimize perioperative care in 100 RC patients; 45 complications occurred in 36 patients (within 30 days), with 16 patients experiencing GI complications, most commonly POI (12 %). The fast-track protocol was deemed favorable in regard to the return of bowel function [5]. In this study, the main components of perioperative modification were no postoperative NGT, use of ketorolac for pain control, gum chewing, and early feeding. Studies from Europe have also shown that POI is less common in patients on an ERAS protocol compared to conservative regimens (15 vs. 28 %), same as subjective constipation [31•]. Their protocol included minimal bowel preparation, high calorie drink the day before up to 2-h pre-operatively, no gastric tube postoperatively, early feeding, and use of prokinetics [31•]. Our group (USC) reported an ERAS protocol in 110 consecutive RC patients, with only 7 cases (6 %) of POI or partial bowel obstruction (PBO) within 30 days after surgery. An NGT was placed in 5 cases and only 2 required total parenteral nutrition (TPN). The data was collected prospectively and not through retrospective chart review. The essential components of the ERAS protocol in our study were no bowel preparation, optimization of perioperative fluid intake, decreased narcotic use, early feeding and mobilization, and use of alvimopan, cholinergic, and prokinetics. These steps decreased median time to bowel function and use of regular diet (2 days) and decreased LOS from a median of 8 to 4 days [2•]. We have since implemented an even earlier time to regular diet on postoperative day 1. A recent review of GI complications from our center with over 300 patients showed that 13 % of RC patients with ERAS protocol developed at least one GI complication, which was significantly lower than the 27 % with traditional pathway [unpublished data]. Focusing on pain management, patients on our enhanced recovery protocol used significantly less opioids per day (4.9 vs. 20.67 mg morphine equivalents, $p < 0.001$) that may have even further contributed to the decrease in POI in this population [32]. Although there is no standard ERAS protocol for RC patients, it appears that decreasing GI complications requires the use of multiple evidence-based interventions as seen in our study [2•].

Ramirez and colleagues reported the incidence of POI across their systematic review as around 10 %; that is lower with some evidence-based steps of ERAS than other studies. They advocated that the best method of reporting POI would be capturing the secondary quantifiers, such as time to flatus, bowel movement, and oral intake, as well as LOS. Age and body mass index were shown to be risk factors for POI [8]. They also demonstrated some evidence in favor of robotic approach and readaptation of the peritoneum to be associated with less POI although it is difficult to rule out observational bias in these studies. GI complications have been reported in about 14.1 % (up to 27 % in 90 days) after robotic-assisted RC, most commonly POI/PBO, followed by enterocolitis and diarrhea [4]. Also in retrospective studies, intracorporeal diversion has been shown to be associated with less GI complications than extracorporeal ones [33].

In summary, the recommended evidence-based steps that may help with GI recovery after RC include no bowel preparation, meticulous intraoperative fluid management, μ-receptor antagonist (alvimopan), cholinergics and prokinetics, early feeding, and mobilization with focus on non-narcotic pain management.

(b) Diarrhea (infectious, non-infectious)

There is paucity of data in the literature on other uncommon GI complications after RC. Reviewing the NSQIP (National Surgical Quality Improvement Program) dataset of 2538 RC patients (1991–2002), colitis (mainly diarrhea) was reported in 0.6 % of patients during their hospital course [34]. Stimson et al. reviewed 90-day re-admission rate after RC and GI-related causes including diarrhea (5 %), ileus (12 %), nausea and vomiting (14 %), and SBO (8 %) were among the most common causes [6]. Novotny et al reported enterocolitis in 2 % of 516 RC patients within 30 days after surgery [35]. In a review by Lawrentschuk et al., the incidence of post RC enterocolitis/persistent diarrhea was 0–8 %; emesis/gastritis/ulcer was reported in 16 %, bowel obstruction in 7 %, and GI bleeding in 1.3 % [36]. In Pruthi et al. study on 100 patients with fast-track protocol, only 1 case (1 %) had infectious enterocolitis [5]. In Maffezini et al. report on 68 patients with enhanced recovery protocol after RC and Indiana pouch, only 2/68 developed infectious enterocolitis [37]. In a recent review of our cohort (169 ERAS patients) for GI complication, diarrhea was reported in 4 (2 %) and infectious enterocolitis in 4 (2 %) during 90-day after RC [unpublished data]. Reviewing the literature and our experience, we recommend probiotic-containing diet and avoidance of antibiotics (that are commonly associated with infectious enterocolitis) after RC. Long-term diarrhea or loose stools is managed with bulking agents such as cholestyramine.

(c) Persistent nausea and vomiting

While modern anesthesia and the use of highly effective medications have significantly reduced the immediate

postoperative nausea, prolonged nausea and vomiting continue to be a source of morbidity following RC and urinary diversion. In the modern ERAS era, Pruthi et al. reported nausea and vomiting collectively with ileus in 12/100 cases on fast-track protocol [5]. Cerantola et al. showed that nonsmokers, female patients, and history of motion sickness increase the chance of postoperative nausea and vomiting. Narcotics, anesthesia, and N2O agent contribute to GI intolerance after RC [19]. Routine use of prokinetics such as metoclopramide has been shown to decrease the chance of nausea after RC. Also, intraoperative fluid optimization can decrease nausea at 24–48 h after surgery [26].

(d) Other GI-related complication

Constipation is defined as inability to have a bowel movement by postoperative day 5 with no signs of ileus or small bowel obstruction [3]. From a review of 1142 patients undergoing RC at Memorial Sloan Kettering, 7 % developed SBO, 3 % were reported to have constipation, 3 % infectious enterocolitis, 1 % bowel leak, and 1 % non-infectious diarrhea [3]. In a study by Novara et al. on complications of RC (174 patients), constipation was reported in 12 % [38]. Bowel leak after RC occurs very rarely, reported at about 0.9 % in Shabsigh study [3] and 2 % in Novara study [38]. In our experience, constipation is a very common long-term complication of urinary diversion and is generally managed with over the counter medications. Increased fiber intake is helpful in regulating bowel movements.

Improvement in QOL

It is difficult to measure quality of life parameters in nonrandomized studies but there is no question that some of the ERAS principles such avoiding bowel preparations and NGT postoperatively lead to an improvement in convalescence. Karl et al reported on a prospective randomized study of early recovery after surgery protocol versus a conservative regimen with the primary endpoint being quality of life. They noted a significant improvement in terms of postoperative morbidity in patients undergoing the enhanced recovery protocol. Patients on the traditional pathway had bowel preparation prior to surgery and a NGT following surgery until bowel movement at which point enteral feeding was resumed. The ERAS pathway lacked the bowel preparation and NG tube and patients resumed fluid intake within 6 h following surgery. While there were no differences noted in the two groups in relation to nausea, emesis, and POI, oral fluid and food intake was higher for patients in the ERAS group on postoperative day 3. It should be noted that alvimopan was not used in this study, which could be responsible for the lack of difference seen in POI. Importantly, however, there was an improvement in the quality of life scores as measured by the validated QLQ-30 (emotional functioning) during hospitalization for the patients in the ERAS group [31•]. One would anticipate that a reduction in nausea, emesis, and POI would further improve quality of life scores.

Cost Effectiveness of ERAS from a GI Standpoint

Cost effectiveness of ERAS protocol has been validated in colorectal as well as RC literature. Since GI morbidity after RC comprises a substantial proportion of perioperative complications, it logically follows a significant source of increased hospital costs. In an economic analysis of the phase 4 double blinded randomized controlled trial of alvimopan following cystectomy, it was shown that POI-related health care cost was $2340 lower for the Alvimopan group, while total combined costs decreased by $2640 per patient for the Alvimopan group versus controls [39]. In our own analysis, we demonstrated an average savings of $4488 per procedure that outweighed the increased drug, home health, and outpatient costs associated with the use of ERAS protocols [40].

Conclusion

Gastrointestinal complications after RC are common and comprise a significant proportion of postoperative morbidity. Ileus remains among the most common complications although the use of enhanced recovery after surgery protocols has shown substantial decrease in GI-related morbidity. Major GI complications including bowel leak, bowel obstruction, and fistulas are rare.

Compliance with Ethical Standards

Conflict of Interest Hooman Djaladat and Siamak Daneshmand each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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