Enhanced Recovery Protocol after Radical Cystectomy for Bladder Cancer

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Purpose: Enhanced recovery after surgery protocols aim to improve patient care and decrease complications and hospital stay. We evaluated our enhanced recovery after surgery protocol, focusing on length of stay, early complication and readmission rates after radical cystectomy for bladder cancer.

Materials and Methods: From May 2012 to July 2013 a perioperative protocol was applied in 126 consecutive patients who underwent open radical cystectomy and urinary diversion. Nonconsenting patients (2), those with previous diversion (2) and prolonged postoperative intubation (3), and those who underwent additional surgery (9) were excluded from study. The protocol focuses on avoiding bowel preparation and nasogastric tube, early feeding, nonnarcotic pain management and the use of cholinergic and μ-opioid antagonists. Outcomes were compared to those in matched controls from our bladder cancer database.

Results: A total of 110 patients with a median age of 69 years were included in analysis, of whom 68% underwent continent urinary diversion. Of the patients 82% had a bowel movement by postoperative day 2. Median length of stay was 4 days. The 30-day minor and major complication rates were 64% and 14%, respectively. The most common minor complication was anemia requiring transfusion in 19% of patients, urinary tract infection in 13% and dehydration in 10%. The latter 2 complications were the most common etiologies for readmission. The 30-day readmission rate was 21% (23 patients). Patients 75 years old or older had a longer length of stay (5 vs 4 days, p = 0.03) and a higher minor complication rate (72% vs 51%, p = 0.04) than younger patients.

Conclusions: Our enhanced recovery after surgery protocol expedites bowel function recovery and shortens hospital stay after RC and urinary diversion without an increase in the hospital readmission rates.

Key Words: urinary bladder, urinary bladder neoplasms, cystectomy, patient readmission, recovery of function

Radical cystectomy, the gold standard treatment for muscle invasive bladder cancer, is among the most complex urological operations and it is associated with considerable morbidity and lengthy hospital stay.1 Improvements in surgical technique, anesthesia and perioperative care have decreased morbidity and LOS, although the mean stay at most centers is still as high as 9 to 11 days.1-3 The mean stay in a recent European series was 17.4 days.4 A population based study and a prospective,
randomized trial comparing open vs robotic RC revealed no significant difference in the overall complication rate\(^4\) or LOS,\(^5,6\) suggesting that perioperative management may have more impact than surgical approach.

ERAS protocols are evidence-based multimodal pathways that optimize the perioperative care of patients undergoing complex surgeries. The goal is to promote acute recovery as demonstrated by decreased LOS with no negative impact on the complication or readmission rate. ERAS protocols, first introduced in patients undergoing colectomy, include perioperative changes in management, including reduced preoperative fasting and early postoperative feeding.\(^5\) Results showed decreased postoperative complications and faster recovery.\(^6\)

There is limited adoption of ERAS protocols for major urological surgeries such as RC. This is most likely multifactorial and may include persistent surgical dogma and/or the belief that urinary diversion is a more complex operation than colorectal surgery with a higher incidence of gastrointestinal complications.\(^7\) The main reason for prolonged LOS after cystectomy remains gastrointestinal morbidity, mostly paralytic ileus.\(^8\) Previous investigators described standardized perioperative care for patients treated with RC with some reduction in LOS.\(^7,9–13\) We describe our ERAS protocol after RC and urinary diversion, focusing on LOS, and readmission and complication rates.

MATERIALS AND METHODS

Study Population

All consecutive patients who underwent open RC, pelvic node dissection and urinary diversion from May 2012 to July 2013 at our institution were enrolled in a prospective, institutional review board approved study. Patients who needed an adjunctive procedure (ie nephroureterectomy) or who remained intubated postoperatively and could not be started on oral feeding per protocol were excluded from analysis. The ERAS protocol was designed to be applied at 3 time points (see Appendix).

Preoperative

Patients were advised to continue a regular diet up to the night before surgery. A high protein, high carbohydrate supplement was recommended the day before surgery. No bowel preparation was used unless urinary diversion involving part of the large bowel was planned preoperatively, in which case only mechanical bowel preparation was recommended. An antibiotic was started intravenously just before the operation and continued for 24 hours.

Intraoperative

The peripherally acting \(\mu\)-opioid antagonist alvimopan was started an hour preoperatively. Intraoperative fluid intake was minimized while the ureters were clipped. Intravascular fluid volume was monitored by stroke volume or central venous pressure. No epidural analgesia was used. Intravenous acetaminophen acetate was started intraoperatively and narcotic use was kept to a minimum. The nasogastric tube was removed at the end of surgery and the patient was extubated unless medically recommended to remain intubated. The patient was transferred to the floor unless there was a medical indication for admission to the intensive care unit.

Postoperative

Bowel function. Alvimopan was continued postoperatively. Neostigmine was also administered under cardiac monitoring. Neostigmine and alvimopan were discontinued after the patient achieved a bowel movement. Oral magnesium based lactulose or bisacodyl suppository was started on POD 1. Prophylaxis for stress ulcers (proton pump inhibitor and H2 receptor blocker) and nausea/vomiting (ondansetron and/or metoclopramide) was administered regularly. Patients were encouraged to ambulate starting on POD 1.

Diet and fluid intake. Patients were started on sips of liquid early after surgery if it was tolerated. On POD 1 a clear liquid diet was started and gradually increased. A regular diet was started on POD 2 in the absence of nausea, vomiting or abdominal distension with a concomitant decrease in intravenous fluid intake. If patient did not tolerate oral food by POD 6 or 7, parenteral feeding was started.

Pain management. Intravenous ketorolac tromethamine and acetaminophen acetate were the mainstays of postoperative pain management unless contraindicated. Paracutaneous subfascial catheters with constant local anesthesia release were also used for local pain control. Oral painkillers were started on POD 1 and most patients were transitioned to oral medication by POD 3. Oral opioid pain medication (oxycodone) was reserved for breakthrough pain.

Discharge and Followup

Patients and caregivers received training at a preoperative educational class and before discharge home. Discharge criteria included 1) adequate pain control, 2) adequate mobility with catheter or stoma care, 3) normal laboratory results, 4) adequate oral intake (1 or more L per day) and 5) bowel movement. In addition, a prophylactic antibiotic was started and continued for 3 weeks or until catheter removal. Starting with patient 25 alkalinization was also added to the protocol if discharge bicarbonate was less than 22 mmol/L. Patients received heparin injections for deep vein thrombosis prophylaxis during hospitalization. Starting with patient 95 the patients were sent home on low molecular weight heparin until POD 28.

Patients were scheduled to return to the clinic 1 week after discharge for the first postoperative visit. To ensure adequate hydration it was arranged for patients to receive a 1 L bolus of intravenous fluid every other day at home or at the nursing facility depending on patient placement after hospital discharge.
Data Collection and Analysis
Patient data were captured prospectively, including details on hospital stay, 30-day complications according to the Clavien-Dindo postoperative complication classification system and readmission rates. A matched group of patients who underwent RC and urinary diversion from January 2002 to May 2012 was selected to compare LOS with that of the ERAS cohort. Matching criteria included age, gender, comorbidities, pathological stage and urinary diversion type. Data were analyzed with SPSS®, version 19.0.

RESULTS

Patient Characteristics
At our institution 126 patients underwent RC and urinary diversion between May 2012 and July 2013. A total of 16 patients were excluded from study due to refusal to participate (2), prolonged intubation due to baseline respiratory problems (3), adjunct procedures including nephroureterectomy (3), male urethrectomy (2), total pelvic exenteration (3), repair after intraoperative rectal injury (1) and revision of existing urinary diversion without bowel anastomosis (2). The table lists the characteristics of the final cohort of 110 patients. A total of 40 patients (36%) were 75 years old or older.

Hospital Stay
An orthotopic ileal neobladder was created in 70 patients (64%). A total of 3 urological oncologists performed the operations using the same surgical technique through an infraumbilical incision. Median estimated blood loss was 400 ml (range 100 to 2,500) and median operative time was 342 minutes (range 210 to 617). A total of 23 patients (21%) received blood transfusion intraoperatively and 20 (18%) were transferred to the intensive care unit from the operating room. Median intensive care unit stay was 2 days (range 1 to 3).

The table also lists details on our ERAS protocol outcomes. Neostigmine was discontinued in 3 patients due to abnormal electrocardiogram findings and bradycardia. Only 1 patient did not tolerate a clear liquid diet on POD 1, 87 (79%) tolerated a regular diet on POD 2 and 3 could not be started on a regular diet by POD 4. Of the patients 90 (82%) had a bowel movement on POD 2 and 4 did not have one by POD 4. No or mild pain (visual analog scale less than 4/10) was reported by 47 patients (43%) on POD 1, by 58 (53%) on POD 2 and by 76 (69%) at discharge. Median LOS in the entire cohort was 4 days (range 3 to 15). A total of 63 patients (57%) were discharged at or before POD 4 while 18 (16%) and 45 (41%) were discharged on PODs 3 and 4, respectively. Median LOS was significantly lower in the ERAS cohort than in matched controls (4 vs 8 days, p < 0.001, see figure).
Time to bowel movement did not differ in different age or urinary diversion groups. Patients 75 years old or older had longer median LOS than their younger counterparts (5 vs 4 days, \( p = 0.03 \)). Urinary diversion type and neoadjuvant chemotherapy had no effect on LOS.

**Complications**
Within the first 30 days postoperatively 72 patients (65\%) experienced at least 1 complication and 40 (36\%) experienced 2 or more. Median time to first complication was 3 days (range 0 to 27). The 30-day minor and major complication rates were 64\% (71 patients) and 14\% (15), respectively. The most common complications were anemia requiring blood transfusion (21 patients or 19\%), urinary tract infection (14 or 13\%) and dehydration (11 or 10\%) (supplementary table 1, [http://jurology.com/](http://jurology.com/)). Seven patients (6\%) were diagnosed with POI and/or partial small bowel obstruction. A nasogastric tube was placed in 5 patients and 2 needed TPN.

Major medical complications included arrhythmia in 9 patients, urosepsis, pulmonary emboli and acute renal failure in 2 each, and respiratory distress, heart failure and transient ischemic attack in 1 each. Complications requiring surgical intervention were bowel evisceration, drain site bleeding, neobladder-vaginal fistula and false passage with continent cutaneous diversion. Compared to younger patients those 75 years old or older had a significantly higher minor complication rate (72\% vs 51\%, \( p = 0.04 \)) and there was a trend toward statistical significance for overall and major complication rates (72\% vs 54\%, \( p = 0.07 \) and 23\% vs 9\%, \( p = 0.05 \)). There was no difference in complication rates with respect to urinary diversion type.

**Readmission**
A total of 92 patients (84\%) were discharged home and 18 (16\%) were discharged to a skilled nursing facility. Due to insurance noncompliance and/or patient refusal 35 (32\%) patients did not receive intravenous hydration at home. Within the first 30 days postoperatively 39 patients (35\%) had at least 1 unscheduled outpatient visit. Median time from discharge to outpatient visit was 6 days (range 1 to 25). The 30-day readmission rate was 21\% (23 patients). Nine patients (8\%) had more than 1 readmission during the first 30 days. Median time from discharge to readmission was 11 days (range 1 to 25). Median LOS on readmission was 3 days (range 1 to 9). Dehydration and urinary tract infection were the most common reasons for 30-day readmission (supplementary table 2, [http://jurology.com/](http://jurology.com/)). Home intravenous hydration status, age and urinary diversion type had no effect on the readmission rate.

**DISCUSSION**
Evidence-based development and implementation of ERAS protocols for patients treated with open RC and urinary diversion can potentially decrease LOS, postoperative pain and morbidity, optimizing convalescence and lowering health care costs.\(^5\) Our initial experience with our ERAS protocol has reduced median LOS from 8 to 4 days without increasing complication and readmission rates. This may be attributable to no preoperative bowel preparation, minimization of perioperative fluid intake, decreased narcotic use, early feeding and mobilization, and the use of alvimopan, cholinergics and prokinetics (see Appendix). They may contribute to early return of bowel function, allowing patients to tolerate regular food and prepare them for discharge. We believe that our standardized surgical protocol and experience along with steps in our ERAS pathway lead to improved perioperative outcomes. While most steps incorporated into our pathway have substantial medical evidence, combined and meticulous application in patients undergoing cystectomy allows optimized results.

Median LOS in our ERAS pathway patients was significantly shorter than in our experience with patients not on the pathway (median LOS 8 days) and those in other fast track programs in the United States (median 5 days) and Europe (13 to 18 days).\(^9\)–\(^13\) However, longer hospitalization in Europe may be due to local reimbursement/cultural differences. Shorter LOS in our patients may have been the result of several early milestones that may be attributable to the ERAS pathway. Another argument would be that the concerted team effort in sending patients home earlier might also have a role in shorter LOS. Given the objective discharge criteria and considerable 4-day difference in median LOS between the 2 groups, the team effort was most likely not a major contributor to the difference seen in the outcome. Median time to ambulation was 1 day, shorter than in other reports.\(^12\) Median time to bowel movement was 2 days, comparable to that of some protocols\(^11\) but substantially shorter than for most others (6 days).\(^10\) Median time to regular diet was 2 days, also shorter than for other protocols implemented in patients undergoing RC (4 days).\(^11,\(^13\)

Preoperative patient counseling on expectations with early discharge can decrease postoperative complications.\(^14\) We advocate avoiding mechanical bowel preparation unless there is a plan to use large bowel since studies show that this does not impact the incidence of wound infection, reoperation or mortality.\(^15\) In addition to opioid sparing anesthesia and limiting fluid administration perioperatively, minimizing the incision to the infraumbilical region
may lead to less pain and better control by local anesthesia through subfascial catheters. Our evolving surgical experience with reduced blood loss may have also hastened postoperative recovery.

After cystectomy nasogastric decompression has been thought to protect bowel anastomosis, prevent emesis and possible aspiration. However, evidence suggests that early nasogastric tube removal with metoclopramide can hasten bowel function recovery and decrease pulmonary complications.16–18 Metoclopramide can also reduce postoperative nausea and emesis, and help early tolerance of solid foods.19 POI, a common cause of prolonged LOS after cystectomy, can be the result of peristaltic impairment due to bowel manipulation and resection.20,21 In our experience the nasogastric tube reinsertion rate was 5% and no patient required reintubation. Alvimopan decreases the incidence of gastrointestinal complications, postoperative morbidity, LOS and estimated costs.22–24 Our use of alvimopan may be partly responsible for reduced median time to flatus and/or bowel movement.

Cardiovascular complications developed in 15 patients (13%). We observed no myocardial infarction in our series. However, there are other medications with well-known cardiovascular side effects in our protocol, such as neostigmine. It is difficult to determine whether the reported cardiovascular events in our series were related to any medication. Neostigmine can also promote bowel motility.25 Decreased POI in our experience also led to a significantly decreased need for TPN with only 2 patients receiving TPN postoperatively. Non-narcotic analgesia using ketorolac can decrease narcotic demand and hasten return of myoelectrical activity after laparotomy.6,26 Early mobilization and reestablishment of a normal diet postoperatively was also encouraged in our patients. An early oral diet is not associated with an increased incidence of postoperative intestinal related sequelae and it can positively impact early recovery and discharge.8,27

Early post-cystectomy complications and readmissions are often underreported in retrospective cohorts due to the nature of followup. Given the prospective nature of this study and the meticulous followup schedule, no patient was lost to followup during the study period. Therefore, although we found no significant difference between the ERAS group and controls regarding the complication rate (65% vs 64%, p = 0.9) or readmission rate (21% vs 18%, p = 0.1), it seems that head-to-head comparison would be misleading since 14% of patients experienced a major complication. The rate of POI and/or partial small bowel obstruction was 6%, substantially lower than for routine management and other fast track studies.1,9,21,28 The early readmission rate in our ERAS cohort is also comparable to that in the randomized trial of the Studer pouch vs the T pouch at our institution (22.6%)29 and experience at other large centers.1 Although there was a trend toward a lower readmission rate in patients who received intravenous hydration at home (20% vs 25%), larger sample size is needed to determine any potential benefits of home intravenous hydration on the readmission rate. Median LOS after readmission was 3 days, and dehydration and urinary tract infection were the most common etiologies, similar to our previous experience. Overall this suggests that our perioperative management was successful in decreasing LOS without increasing the readmission rate.

Although this was a prospective study with dedicated followup, a randomized, controlled trial would provide the most definitive evidence in this regard. However, blinding and determining the main randomization factor among multiple existing modifications in the protocol would be challenging issues for a randomized, controlled trial. Strict protocol adherence, especially home intravenous hydration, was not accomplished in all patients due to insurance restrictions and patient convenience. The study is also limited by its sample size, although these initial observations prompted us to begin this protocol in all patients undergoing cystectomy at our center. Although interventions such as alvimopan, neostigmine with cardiac monitoring and home intravenous hydration add some cost to the total cost of cystectomy care, an average 2.6-day decrease in LOS after using alvimopan alone in patients who undergo cystectomy can lower the total health care cost more than $2,600,30 which is much higher than the estimated cost of interventions in our study. Cost-effective analysis would provide more definitive evidence in this regard but it was beyond the scope of this study.

CONCLUSIONS
Our ERAS protocol uses perioperative evidence-based management modifications to improve the postoperative care and recovery of patients undergoing RC and urinary diversion for bladder cancer. The protocol is feasible and safe in most patients and associated with a significant reduction in LOS without increasing the complication or readmission rate.

APPENDIX
Perioperative Protocol for RC and Urinary Diversion for Bladder Cancer

Preoperative:
- Precystectomy educational class
- Carbohydrate loading
- No bowel preparation
- Alvimopan
- No epidural
REFERENCES


EDITORIAL COMMENT

ERAS seems to be a timely issue as more and more surgical disciplines appreciate the benefits of such programs. The authors found that an ERAS protocol led to a bowel movement on postoperative day 2 in 82% of patients and a median LOS of only 4 days. These are promising results for patients and health care providers.

A certain drawback of the study is that there was no prospective control group, which makes comparison between the new ERAS protocol and the former protocol more difficult.

Apart from the documented faster recovery of ERAS patients our experience shows a further important advantage of such programs, that is improved quality of life after surgery. Especially in these patients this factor seems to have a further important role.

A personal remark on the extensive bowel stimulation presented in this study is that in Europe there are different concerns about using alvimopan due to possible cardiovascular events. The authors state that 15 patients (13%) had cardiovascular complications within the first 30 days. As the authors also used another approach to overcome this problem, it is difficult to judge what exactly caused these events. It may be possible to use only mild laxatives postoperatively in the first place and change to other substances only when really necessary.

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REPLY BY AUTHORS

We agree that a randomized trial would provide the most definitive evidence in this regard. However, the main objective of the current pilot study was to show the feasibility and efficacy of our institution specific perioperative protocol to set the stage for a multi-institutional, prospective study in the future. Nevertheless, the substantial difference in the outcome, specifically time to bowel activity and LOS, compared to the carefully matched control group makes our results convincing enough to be used as strong evidence for the efficacy of the protocol. We also agree that another advantage of the protocol is the significant improvement in quality of life, although this was not measured in our study, with the avoidance of nasogastric tubes and bowel preparation, and the introduction of early feeding.

With regard to alvimopan the recently published randomized phase 4 study in patients undergoing RC showed no significant difference between the alvimopan and placebo groups in cardiovascular events (reference 24 in article). The rate of cardiovascular events in our study may have been due in part to intense cardiac monitoring during the hospital stay and it is not significantly different from that in our prior reported results. Results from 5 multicenter, double-blind, randomized, placebo controlled trials including 1,877 patients as well as a meta-analysis of 3 of the trials including a pooled modified intent to treat population of 1,388 have documented the benefits of alvimopan in reducing time to bowel recovery and hospital discharge in patients treated with abdominal surgery. Laxatives have been used for the last 30 years at our institution and remain a part of our postoperative bowel regimen but they have not been shown to decrease the ileus rate. Therefore, we strongly believe that adding alvimopan to an accelerated recovery program is a major contributor to our results and concerns for cardiovascular events should not prompt any changes in the protocol.

REFERENCE