Clinics in Oncology

Research Article
Published: 23 Mar, 2017

Feasibility of a Fast-Track Cystectomy Program

Per Bagi[1], Peter Thind[1], Lisbeth Salling[1], Martin Skønnemand[2] Susann Vellier Hansen[1] and Henrik Kehlet[3]*

[1]*Department of Urology, Copenhagen University, Denmark*

[2]*Department of Anestesiology, Copenhagen University, Denmark*

[3]*Department of Surgical Pathophysiology, Copenhagen University, Denmark*

Abstract

Introduction: Enhanced Recovery After Surgery (ERAS) has consistently led to decreased need for hospitalisation and risk of complications without increased readmission rates. ERAS has recently spread to Radical Cystectomy (RC), but so far with limited data.

Methods: We introduced an aggressive ERAS program for RC as one step. The results from two cohorts, each consisting of 25 consecutive patients undergoing RC before and after introducing our ERAS program were compared. The ERAS program focused on preoperative education of patient and intra-/postoperative care, with normovolemia, accelerating mobilization and removal of gastric tube facilitating early oral feeding. Analgesia was secured by local anaesthesia, avoiding epidural, and low dose opioid, combined non-opioid analgesics and antiemetics, including high-dose preoperative methylprednisolone.

LOS was reduced from 7 to 4 days, and positive fluid balance and duration of nasogastric suction were reduced ($p<0.05$) after introducing ERAS. In-hospital rate of serious complications (Clavien-Dindo grade above 2) was 6%, similar in both groups. After 90 days, 1 patient had died, and further 14 patients (28%) suffered serious complications. Readmission occurred in 22 patients (44%), but one third required no or minor non-surgical intervention, similar in both groups. There was no difference in outcomes between open *vs.* robot-assisted RC.

Conclusions: Introduction of an aggressive RC ERAS program reduced LOS to about 4 days without increasing morbidity or readmissions, calling for future large-scale safety studies.

Introduction

Fast-track or Enhanced Recovery After Surgery (ERAS) programs have been developed during the last 20 years in a variety of procedures [1] and consistently leading to decreased need for hospitalisation, risk of medical complications and without increased readmission rates. Although most scientific and well-documented outcomes originally came from colorectal procedures, the success has spread to major urological procedures including cystectomy [2-4]. However, a review on ERAS programs for cystectomy concluded that data were limited, but that translational data from similar procedures were so encouraging that future studies should be done [2] and as emphasised in a recent consensus review [5]. Consequently, several programs have been developed, but with a variable emphasis on the different multimodal components of a fast-track program and most often as observational studies. However, despite the agreement that an RCT may be a gold standard in clinical research in developing areas of interest, a detailed prospective observational study may be appropriate [6]. The data from recent reported fast-track cystectomy programs are variable with a reported length of stay (LOS) between 3 days in one 30 patient robotic cystectomy study [7] but otherwise between 7-9 days [2-4,7-12] and with different programs and often lacking full implementation of the important components documented in colorectal procedures including opioid-sparing multimodal analgesia, focus on avoiding a fluid overload or hypovolaemia, early mobilisation, anti-ileus regimens etc. The topic is getting even more complicated after the introduction of robot-assisted cystectomy [2,7,10,13-15] and so far with inconclusive results in a fully implemented fast-track program.

The aim of the present 2-stage combined retrospective – prospective setup was to assess an aggressive fast-track cystectomy program regarding feasibility and safety, serving as a basis for a subsequent RCT or comparative robot *vs.* open setup.

Material and Methods

In August 2015 an ERAS protocol for patients undergoing radical cystectomy (RC) for

OPEN ACCESS

Correspondence:
Per Bagi, Department of Urology D2112, Rigshospitalet, Blegdamsvej 9, DK-2100, Copenhagen Ø, Denmark, E-mail: per.bagi@regionh.dk

Received Date: *19 Dec 2016*
Accepted Date: *16 Feb 2017*
Published Date: *23 Mar 2017*

Citation:
Bagi P, Thind P, Salling L, Skønnemand M, Vellier Hansen S, Kehlet H. Feasibility of a Fast-Track Cystectomy Program. Clin Oncol. 2017; 2: 1243.

Table 1: Differences in Pre-ERAS and Post-ERAS programs.

	Pre-ERAS	Post-ERAS
Pre-operative	Standard verbal and written information by the surgeon.	Extensive verbal information by the surgeon and specialist nurse, including surgical details, hospital stay, expectations for each day, stoma education and patient expectations. Supplementary written information, including flow sheet expectations for the hospital stay, is handed out.
Intra-operative	On the morning of surgery: Ondansetrone 4 mg and Dexamethasone 8 mg, on individual indication. Antibiotics for 3 days (cefuroxime 1.5 g x 2 and metronidazole 0.5 g x 3) started at induction of anaesthesia. Lactated Ringers solution as a crystalloid and Human Albumin 5% as a colloid administrated as IV drip in no predetermined pace. Human albumin as substitution to bleeding not meeting the transfusion criteria. At end of surgery infusion of bupivacaine/morphine in thoracic epidural catheter for 3 days.	On the morning of surgery: Oxycodone 20 mg; Ibuprofen 600 mg; Gabapentin 600 mg. Methylprednisolone 125 mg iv. Antibiotics (cefuroxime 3 g) at induction of anaesthesia. Arterial line and beat to beat monitoring of stroke volume, systemic vascular resistance and cardiac output using Flow-trac/Nexfin. Fluid therapy intra-operatively and during PACU stay followed the principles of Gold Directed Fluid Therapy, GDFT [17]. Basic infusion and lactate Ringer`s solution 1.5 ml/kg/h. Stroke Volume (SV) optimized by bolus Human Albumin 5% (HA) 250 ml. A 10 % increase in SV on fluid bolus or a 10% decrease from optimal SV triggered a fluid bolus. The SV were kept at an optimum from continuous monitoring and repeated HA boluses as needed. Tranexamic acid 1 g. At end of surgery local anaesthesia bupivacaine 2 mg/kg in subcutaneous, fascial and muscular wound layers. Paracetamol 1 g; Morphine 0.2 mg/kg; Ondansetrone 4 mg.
Postoperative	Ondansetrone 4mg on individual indication. Opioid treatment on individual indication. Mobilization when patient feels comfortable. Nasogastric tube removed after passing gas. Oral feeding after passing gas. Discharge after bowel movement, mobilized and able to drink and eat. Follow-up in out-patient clinic after 3 weeks.	Oxycodone 20 mg*2; Gabapentin 300+600 mg; Ibuprofen 600 mg 8-hourly; Paracetamol 1 g 6-hourly. Metoclopramide 10 mg 8-hourly. Ondansetrone 4 mg on indication. Removal of central venous line on PACU discharge. Early mobilization, starting at day of surgery, following standardized plan. Nasogastric tube removed day after surgery if tolerating 6 h closure. Oral feeding, liquid at day of surgery, full diet as tolerated. Discharge when mobilized and able to drink. Follow-up by phone 3-5 days after discharge, and in out-patient clinic after 3 weeks.

bladder neoplasia was introduced at Rigshospitalet, Copenhagen. A retrospective analysis of 25 consecutive patients undergoing RC from March to July 2015 (Pre-ERAS cohort) and 25 prospective consecutive patients from August to October 2015 (Post-ERAS cohort) was performed. Two patients operated after the Pre-ERAS regime ended, acted as run-out patients for the Pre-ERAS regime/run-in patients for the Post-ERAS regime, and were not included in the study. Details on differences in perioperative care according to the Pre-ERAS *vs.* Post-ERAS programs appear from Table 1. Significant parts of the perioperative regime including surgical technique, being robot-assisted or open RC, as well as urinary diversion were standardized for all patients, and remained unchanged during the study period. 1) Pre-operatively, any medical co-morbidity were addressed and optimized if relevant. The patients were fasting 6 h for solid foods and 2 h for liquids and had a phosphate enema at the morning of surgery. No mechanical bowel preparation was applied. Before induction of anaesthesia the patient received iv 125 mg methylprednisolone due to the previously demonstrated positive recover effect [16]. 2) Intra-operatively the patients had Deep Venous Thrombosis (DVT) prophylaxis using TED-stockings and low molecular weight heparin to be continued for 1 month postoperatively. General anaesthesia was induced using propofol and remifentanil supported by cicatracurium. All patients had an intraoperative nasogastric tube. Surgery included removal of the bladder, prostate and seminal vesicles in men and bladder, uterus, anterior vaginal wall and adnexae in women. For both genders pelvic lymph node dissection was performed including common and external iliac and obturator nodes bilaterally. Nephroureterectomy or pelvic exenteration was performed on specific indication. Urine diversion was performed as ileal conduit, pouch or neobladder, according to the surgeon's recommendations and patient's request. The transfusion trigger was Hb 4.3 mM or uncontrolled bleeding. For patients with pre-existing cardiac disease the trigger was 5mM. A drain was placed close to ureteric anastomoses. 3) Post-operatively patients stayed at the PACU until the morning after surgery. The tube drain was removed when producing less than 50 ml, and ureteric tubes were removed after 1 week. All patients were offered chewing gum.

Statistical analysis

Quantitative parameters were compared using the Mann-Whitney test, and binomial results were compared using Fischer's exact test. Calculations were based on two-sided tests, and level of significance was chosen as 0.05.

Results

Both the Pre-ERAS and Post-ERAS regime were applied to all patients according to time of surgery, irrespective of age, cancer stage or comorbidity. Patient demographics and details on pathology and surgery are given in Table 2, and perioperative details in Table 3. Groups were comparable according to demographics and details on pathology and surgery, as well as duration of surgery, perioperative bleeding and transfusion.

In the Post-ERAS group, fluid administration was guided by the principles of individualized goal directed therapy [17] in order to avoid hypovolaemia and overhydration, and the fluid balance at end of surgery showed a significantly lower fluid administration

Table 2: Gender, age, BMI, American Society of Anesthesiologists score (ASA), surgical technique, urinary diversion and pathology.

	Pre-ERAS	Post-ERAS	p
Gender (male/female)	19/6	19/6	ns
Age (years), median (range)	70(49-79)	68(33-82)	ns
BMI (kg/m^2), median (range)	24.7(15.3-35.6)	25.4(18.0-46.3)	ns
ASA score 1-2 / 3-4	14/11	14/11	ns
Open RC Robot-assisted RC	15 10	16 9	ns
Preoperative neoadjuvant chemotherapy	8	5	ns
RC RC and nephroureterectomy RC and pelvic exenteration	24 1 0	23 1 1	ns
Urinary diversion Ileal conduit Neobladder Pouch Ureterocutaneostomy	 24 0 0 1	 21 3 1 0	ns
Pathology Urothelial/sarcomatoid+sqamous ≤pT1a pT1b pT2 pT3 pT4 Positive lymph nodes	 23/2 2 8 6 6 3 7	 23/2 3 10 7 3 2 3	 ns ns ns
Positive surgical margins	1	0	ns

Table 3: Perioperative data.

	Pre-ERAS	Post-ERAS	p
Operative duration, (min), median (range) Open RC (min), median (range) Robot-assisted RC (min), median (range)	220 (140-406) 188 (140-312) 285 (241-406)	230 (125-513) 180 (125-317) 354 (289-513)	ns
Intraoperative bleeding, (ml), median (range)	700 (100-1750)	650 (100-2600)	ns
Intraoperative fluid balance, (ml), median (range)	+ 1970 (250-3000)	+ 700 (-700-2450)	<0.01
Transfusion (units) 0 1 3 4 5	 20 3 1 0 1	 20 3 1 1 0	 ns

in the Post-ERAS group (p <0.01) (Table 3). The use of continued nasogastric suction was reduced from 2 days to 1 day (p <0.01) in the Post-ERAS group. Implementation of the Post-ERAS regime allowed the patients to be mobilized earlier and to return to regular oral diet. The median LOS was reduced from 7 to 4 days (p <0.01).

Complications showed no differences between groups. Thus, during hospitalization 56% in the Pre-ERAS group and 76% in the Post-ERAS group suffered no complications according to the Clavien-Dindo classification, and the majority of patients (96%) suffered no or only minor complications, grade 1 or 2. Two patients had major complications grade 3 (fascial dehiscence) or 4 (septicaemia).

The readmission rate within 90 days was 44%, with a median length of stay of 4 days, ranging from 1 to 71 days (p> 0.05 between groups). Reasons for re-admissions are given in Table 4. In 8 of the readmitted patients, 36% in both groups, no intervention, or only minor changes in medication were indicated. After 90 days 36% in the Pre-ERAS group and 44% in the Post-ERAS group suffered no complications according to the Clavien-Dindo classification, and the majority of patients (70%) suffered no or only minor complications, grade 1 or 2. Although 15 patients had grade 3 to 5 complications, amongst whom 1 died (Table 4), there were no differences between the groups.

When separating the Pre- ERAS and Post-ERAS groups according to surgical technique (open or robot-assisted), no differences were found in LOS, morbidity and readmissions (data not shown).

Discussion

The main goal of ERAS programs is to optimize perioperative care in order to improve patient recovery as indicated by decrease in LOS with no negative effect on complications nor re-admission rate [1,2,8]. In the present study an aggressive one step ERAS program was introduced with simultaneous inclusion of all changes and modifications of our standard Pre-ERAS regime. Previous studies have demonstrated a variable feasibility of different ERAS programs [1,3,4,8-10,18]. Our program was revised according to recent literature, and all parts of the standard program were re-evaluated by a multidisciplinary group of health professionals, including surgeons, anaesthesiologist, nurse staff in PACU, outpatient department and ward, stoma care specialist and physiotherapist involved in care and treatment of these patients. Focus for the changes were preoperative education of patient (and relatives), securing a detailed knowledge and rationale for all phases in the program, and expected day to day progress, intra- and postoperative routines, accelerating postoperative mobilization, early removal of the gastric tube and early oral feeding and finally, adjusting anaesthesia avoiding hypovolemia and over

Table 4: Number of complications (Clavien-Dindo) and readmissions within 90 days.

	Pre-ERAS	Post-ERAS	p
Clavien-Dindo (90 days)			
0	9	11	
1	1	1	
2	8	5	
3	6	7	ns
4	1	0	
5	0	1	
Readmissions within 90 days n (%)	10 (40)	12 (48)	ns
Duration of readmission	3(1-71)	5(1-35)	ns
Reason for readmission			
Pain	1	1	
Melaena	0	1	
Suspicion of DVT	1	0	
Superficial wound infection	2	0	
Retention in ilealconduite	0	1	
Urinary tract infection	0	1	
Fascial dehiscence	1	1	
Ureteric retention	1	0	
Leakage from neobladder	0	1	
Lymphocele	2	1	
Fever unknown reason	1	1	
Pelvic abscess	1	1	
Septicemia	0	1	
Vaginal prolapse	0	1	
Aspiration pneumonia, death	0		

hydration. Analgesia was standardised, replacing epidural analgesia by local anaesthetic infiltration in the wound, low dose opioid and intensified non-opioid analgesics and antiemetics, including a high preoperative dose of methyl prednisolone [16]. Consequently, this new multimodal strategy was theoretically aimed to reduce pain and nausea and to improve early mobilization and bowel function.

LOS after RC has traditionally been long and recent European studies report approximately 1-2 weeks, while American studies often report shorter LOS, but without details of discharge location [3,8,18,19]. However, LOS has declined during recent years, and a recent Danish study showed a fall from approximately 2 weeks in 2006 to 9 days in 2013 – still without implying the aggressive principles of ERAS [20]. Consequently, studies comparing ERAS cohorts with historical controls should be taken with care [3,9,18]. In the present study the LOS was 7 days during the Pre-ERAS program, and after the modifications were introduced a decrease in LOS to 4 days was seen.

However, RC is a morbid procedure, and decreasing the need for hospitalization should not be seen as the main target for ERAS programs, but only as one of several required improvements in the patient course [2-4,21,22]. Thus, the major focus should be directed to patient safety. In our program, all patients were contacted by phone by a nurse specialist a few days after leaving hospital, which allowed patients to discuss potential problems and concerns. All patients had free access to the department after discharge if required. Overall, 44 percent of patients were readmitted within 90 days, but with no difference between Pre- and Post-ERAS groups. More than one third of these patients required no treatment or only minor changes in medication during readmission. The readmission rate given in the literature is high, with reported rates up to 40 percent [3,9,18,19,23]. However, the rate of readmission in Denmark may potentially be influenced by organizational issues, as access to hospital is easy in Denmark – and free of any costs – and all readmissions were directed to the operating hospital, in contrast to potential readmissions directed to 'other hospitals', adding up one fifth of readmissions [20,21] and limiting interpretation in many studies.

The majority of complications in the present study were related to wound problems and infection, but the number and character of complications showed no difference between the two groups, nor did they seem related to the ERAS program. One patient died because of aspiration during reoperation for fascial dehiscence resulting in a 90 days mortality of 2 percent, but not different from international series, reporting mortality rates up to 4.5 percent in unselected series, and even higher in elderly and after 90 days [3,4,8,19,21,24]. Current results from all Danish RC's performed from 2006 to 2013 showed a 30-day mortality of 1.3 percent [20], but obviously, documentation of the safety of the Post-ERAS program will require a larger study population.

Most previous studies have introduced ERAS in RC stepwise or only in simple RC with ileal conduit and omitting patients requiring more complicated procedures [3,4,8,11,18]. In the present study, all patients having RC performed during the study period were included. Consequently, 7 patients underwent more complicated surgery; 1 of which was in the Pre-ERAS and 6 in the Post-ERAS cohort. It is well known, that these more extensive procedures are followed by a higher risk of complications. Accordingly, all these 7 patients suffered complications according to Clavien-Dindo classification, ranging from 1-5, median 2; and 5 (71%) of these patients were readmitted within 90 days.

Even though the present ERAS program was introduced fully in one step, this does not preclude later adjustments and improvements. Classically, ERAS are described as an extensive program, including more than 20 individual elements, but not all these parts were included in our program according to previous debates [1-3,8,10]. However, after the initial positive results given herein, revision of our ERAS program is planned, considering omitting postoperative drainage and nasogastric suction [2-4,8,10,18].

During recent years robot-assisted RC has been introduced rapidly, and even though minimal invasive technique from a theoretically point of view should reduce surgical stress and trauma, this has not currently translated into improved outcome after RC [2,7,10,13,14]. The present study was not designed to demonstrate any difference between classical open RC and robot-assisted RC, but when data were split up between these 2 techniques no difference in end-points could be demonstrated.

In conclusion, introduction of an aggressive RC ERAS program reduced LOS from 7 to 4 days without increasing morbidity or readmissions, calling for large-scale detailed outcome studies.

References

1. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg. 2008;248(2):189-98.
2. 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(2):263-6.
3. Smith J, Meng ZW, Lockyer R, Dudderidge T, McGrath J, Hayes M, et al. Evolution of the Southampton Enhanced Recovery Programme for radical cystectomy and the aggregation of marginal gains. BJU Int. 2014;114(3):375-83.
4. 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(2):335-40.

5. 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(4):649–660.
6. Berwick DM. The science of improvement. JAMA. 2008;299(10):1182-4.
7. Shah AD, Abaza R. Clinical pathway for 3-day stay after robot-assisted cystectomy. J Endourol. 2011;25(8):1253-8.
8. 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.
9. Persson B, Carringer M, Andren O, Andersson SO, Carlsson J, Ljungqvist O. Initial experiences with the enhanced recovery after surgery (ERAS) protocol in open radical cystectomy. Scand J Urol. 2015;49:302-7.
10. 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((R))) society recommendations. Clin Nutr. 2013;32:879-87.
11. Baack Kukreja JE, Messing EM, Shah JB. Are we doing "better"? The discrepancy between perception and practice of enhanced recovery after cystectomy principles among urologic oncologists. Urol Oncol. 2016;34(3):120-1.
12. Tyson MD, Chang SS. Enhanced recovery pathways versus standard care after cystectomy: A meta-analysis of the effect on perioperative outcomes. Eur Urol. 2016;70(6):995-1003.
13. Bochner BH, Dalbagni G, Sjoberg DD, Silberstein J, Keren Paz GE, Donat SM, et al. Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: A Randomized Clinical Trial. Eur Urol. 2015;67(6):1042-50.
14. Saar M, Ohlmann CH, Siemer S, Lehmann J, Becker F, Stöckle M, et al. Fast-track rehabilitation after robot-assisted laparoscopic cystectomy accelerates postoperative recovery. BJU Int. 2013;112:E99-106.
15. Adding C, Collins JW, Laurin O, Hosseini A, Wiklund NP. Enhanced recovery protocols (ERP) in robotic cystectomy surgery. Review of current status and trends. Curr Urol Rep. 2015;16(5):32.
16. Lunn TH, Kristensen BB, Andersen LO, Husted H, Otte KS, Gaarn-Larsen L, et al. Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: a randomized, placebo-controlled trial. Br J Anaesth. 2011;106:230-8.
17. Bundgaard-Nielsen M, Ruhnau B, Secher NH, Kehlet H. Flow-related techniques for preoperative goal-directed fluid optimization. Br J Anaesth. 2007;98(1):38-44.
18. Daneshmand S, Ahmadi H, Schuckman AK, Mitra AP, Cai J, Miranda G. Enhanced recovery protocol after radical cystectomy for bladder cancer. J Urol. 2014;192:50-5.
19. Jerlstrom T, Gardmark T, Carringer M, Holmäng S, Liedberg F, Hosseini A, et al. Urinary bladder cancer treated with radical cystectomy: perioperative parameters and early complications prospectively registered in a National population-based database. Scand J Urol. 2014;48:334-40.
20. Bagi P, Nordsten CB, Kehlet H. Cystectomy for bladder cancer in Denmark during the 2006-2013 period. Dan Med J. 2016;63(4).
21. Pak JS, Lascano D, Kabat DH, Finkelstein JB, RoyChoudhury A, DeCastro GJ, et al. Patterns of care for readmission after radical cystectomy in New York State and the effect of care fragmentation. Urol Oncol. 2015;33(10):426.
22. Zakaria AS, Santos F, Dragomir A, Simon Tanguay, Wassim Kassouf, Armen G Aprikian. Postoperative mortality and complications after radical cystectomy for bladder cancer in Quebec: A population-based analysis during the years 2000-2009. Can Urol Assoc J. 2014;8:259-67.
23. Aghazadeh MA, Barocas DA, Salem S, Clark PE, Cookson MS, Davis R, et al. Determining factors for hospital discharge status after radical cystectomy in a large contemporary cohort. J Urol. 2011;185:85-9.
24. Zakaria AS, Santos F, Tanguay S, Kassouf W, Aprikian AG. Radical cystectomy in patients over 80 years old in Quebec: A population-based study of outcomes. J Surg Oncol. 2015;111(7):917-22.