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Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS®) society recommendations

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SUMMARY

Purpose: Enhanced recovery after surgery (ERAS) pathways have significantly reduced complications and length of hospital stay after colorectal procedures. This multimodal concept could probably be partially applied to major urological surgery.
Objectives: The primary objective was to systematically assess the evidence of ERAS single items and protocols applied to cystectomy patients. The secondary objective was to address a grade of recommendation to each item, based on the evidence and, if lacking, on consensus opinion from our ERAS Society working group.
Evidence acquisition: A systematic literature review was performed on ERAS for cystectomy by searching EMBASE and Medline. Relevant articles were selected and quality-assessed by two independent reviewers using the GRADE approach. If no study specific to cystectomy was available for any of the 22 given items, the authors evaluated whether colorectal guidelines could be extrapolated.
Evidence synthesis: Overall, 804 articles were retrieved from electronic databases. Fifteen articles were included in the present systematic review and 7 of 22 ERAS items were studied. Bowel preparation did not improve outcomes. Early nasogastric tube removal reduced morbidity, bowel recovery time and length of hospital stay. Doppler-guided fluid administration allowed for reduced morbidity. A quicker bowel recovery was observed with a multimodal prevention of ileus, including gum chewing, prevention of PONV and minimally invasive surgery.
Conclusions: ERAS has not yet been widely implemented in urology and evidence for individual interventions is limited or unavailable. The experience in other surgical disciplines encourages the development of an ERAS protocol for cystectomy.

1. Introduction

Enhanced recovery after surgery (ERAS) protocols have been introduced to reduce surgical stress and facilitate postoperative

Abbreviation: ERAS, enhanced recovery after surgery; LOS, length of hospital stay; RCT, randomized controlled trial.

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recovery.[1] In colorectal surgery, meta-analyses have provided level 1 evidence (LE) for reduction of complications (−50%) and hospital stay (−2.5 days) by application of ERAS pathways.[2] Thus, ERAS programs constitute comprehensive and evidence based best care in colorectal surgery. Modified ERAS protocols are successfully used in many other specialties including gynecology, thoracic, vascular, pediatric and orthopedic surgery.[3] Interestingly, ERAS protocol development or utilization in urology appears to have a low adoption.

Radical cystectomy represents a significant surgical challenge in urology. Despite standardization of the surgical technique, improved anesthesia and perioperative care protocols, morbidity after open radical cystectomy with bilateral pelvic lymph node dissection and urinary diversion or bladder reconstruction mounts up to 30–64%.[4] Cystectomy patients may be ideal candidates for an ERAS pathway as the potential for reduction of surgical stress and complications is very high. However, uncritical application of the guidelines issued from colorectal procedures[5] seems inappropriate as the surgical procedure itself differs widely (small bowel anastomosis, urine within the peritoneal cavity, both extra- and intraperitoneal access, longer operative time, increased risk of blood loss and transfusions). The most recent recommendations for rectal surgery represent an adjusted protocol and might provide guidance for other pelvic surgeries.[6]

The goal of the present systematic review was to analyze application of ERAS protocols and the evidence for individual ERAS items for cystectomy. Our aim was to provide a comprehensive ERAS pathway for cystectomy based on the available evidence and assimilating recommendations for other pelvic surgeries where appropriate.

2. Evidence acquisition

This systematic review was performed in accordance to the PRISMA statement.[7]

2.1. Data sources and search strategies

Embase and Medline (through Pubmed) were searched systematically using medical subject headings including “cystectomy AND all 22 pre-, intra- and postoperative ERAS items” (Table 1). Electronic links to related articles and references of selected articles were hand-searched. Eligible articles included meta-analyses, randomized controlled trials (RCTs) or prospective case series including a control group published between January 1997 — 1st landmark study on ERAS published[1] — and April 2012, with no language restriction.

2.2. Study selection (inclusion and exclusion criteria)

All types of cystectomy associated with urinary diversion/bladder reconstruction were included. At least one of the following main outcome measures had to be reported: complications, time to return of bowel function (flatus/stool) or length of hospital stay (LOS). Since one goal of this systematic review was to evaluate the impact of individual ERAS items, only single-intervention studies with otherwise identical perioperative care were considered. If more than one ERAS item was implemented in the study group, the study was still included but no level of evidence was attributed to the items because of evident bias.

2.3. Data extraction and quality assessment

Two authors (YC and MV) independently performed the literature search. The entire research team made the final decision on inclusion of a study. The search terms were firstly identified in the title, and secondly in the abstract or medical subject headings. All studies of interest were obtained as full text articles and scrutinized thoroughly. Relevant data were extracted and documented in a database developed a priori for all publications. The methodological quality and internal validity of included RCTs was assessed using the Jadad-score.[8] In accordance to the recently published ERAS guidelines for rectal surgery,[6] the level of evidence for each ERAS items was determined using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, in which the evidence is classified as high, moderate, low or very low[9] (Fig. 1).

3. Evidence synthesis

The electronic search of the literature yielded 804 potential studies. The selection process is displayed in Fig. 2.

Overall, 6 RCTs and 5 prospective controlled case series were analyzed. Median number of patients per group per study was 21 (range 8–51). Overall, the quality of RCTs was low; two had Jadad-scores $\geq$3. Out of the 22 standard single ERAS items, only 7 (oral mechanical bowel preparation, minimally invasive approach, perioperative fluid management, nasogastric intubation, urinary drainage, prevention of postoperative ileus and prevention of PONV) were studied (Table 2). Nine more items (preoperative counseling and education, preoperative fasting, thrombosis prophylaxis, epidural analgesia, resection site drainage, antimicrobial prophylaxis, early oral nutrition, early mobilization and postoperative analgesia) were included in some multimodal approaches (Table 2). However, due to the impossibility to determine which single ERAS item contributed to enhanced outcomes, no level of evidence could be attributed to these items.

Preoperative medical optimization, carbohydrates loading, preanesthesia medication, standard anesthetic protocol, preventing intraoperative hypothermia and audit (6 items) were not studied in cystectomy patients.

The results, level of evidence and grade of recommendations are summarized in the proposed care pathway in Table 1.

3.1. Preoperative items

1. Preoperative counseling and education

There is no study evaluating the therapeutic effect of preoperative patient’s information and counseling on post-cystectomy outcomes. However, it has been shown that thorough information could reduce anxiety, enhance wound healing and postoperative recovery and decrease complications after a variety of abdominal interventions.[10] Special emphasis on stoma education as ostomy is an independent risk factor for delayed discharge within ERAS protocols.[11]

2. Preoperative medical optimization

Medical optimization (i.e. hypertension, anemia and diabetes), physical exercise and cessation of smoking and drugs or alcohol abuse are all considered as preoperative conditioning measures.[6] Even though most of them have been identified as risk factors for complications after cystectomy in a retrospective cohort analysis,[12] there is no available evidence showing that their correction improves outcome.

As far as colorectal surgery is concerned, there is evidence that smoking cessation reduces postoperative morbidity, as well as preoperative optimization of medical conditions and cessation of alcohol intake 4 weeks before surgery. Implementing physical exercise preoperatively may be of benefit.[6]

Table 1
Summary of each ERAS item and their respective level of evidence and grade of recommendation derived from both the cystectomy and the colorectal literature.

ERAS single item	Summary	Specifics for cystectomy patients/ open questions	Evidence for cystectomy/ rectal surgery	Grade of recommendation
1. Preoperative counseling and education	Patients should receive routine dedicated preoperative counseling and education	Surgical details, hospital stay and discharge criteria in oral and written form; stoma education; patient's expectations	Na/Low	Strong
2. Preoperative medical optimization	Preoperative optimization of medical conditions should be recommended. Preoperative nutritional support should be considered, especially for malnourished patients	Correction of anemia and co-morbidities Nutritional support Smoking cessation and reduction of alcohol intake 4 weeks prior to surgery; encouraging physical exercise	Na/Moderate Na/High Na/Moderate Na/Very low	Strong
3. Oral mechanical bowel preparation	Preoperative bowel preparation can be safely omitted	/	Moderate/High	Strong
4. Preoperative carbohydrates loading	Preoperative oral carbohydrate loading should be administered to all non-diabetic patients	/	Na/Low	Strong
5. Preoperative fasting	Intake of clear fluids up until 2 h before induction of general anesthesia is recommended. Solids are allowed up until 6 h before anesthesia.	/	Na/Moderate	Strong
6. Preanasthesia medication	Avoidance of long-acting sedatives	/	Na/Moderate	Strong
7. Thrombosis prophylaxis	Patients should wear well-fitting compression stockings, and receive pharmacological prophylaxis with LMWH. Extended prophylaxis for 4 weeks should be carried out in patients at risk. 12 h interval between injections and epidural manipulation.	Cystectomy patients are considered at risk; prolonged prophylaxis should therefore be administered	Na/High	Strong
8. Epidural analgesia	Thoracic epidural analgesia is superior to systemic opioids in relieving pain. It should be continued for 72 h	/	Na/High	Strong
9. Minimally invasive approach	At most feasible; in trial setting Long term oncological results awaited	Laparoscopic/robotic cystectomy is not recommended outside a trial setting until long term results are available.	Low/Moderate	Strong
10. Resection site drainage	Perianastomotic and/or pelvic drain can be safely omitted	Because of urine leak, drainage might be required in cystectomy patients	Na/Low	Weak
11. Antimicrobial prophylaxis and skin preparation	Patient should receive a single dose antimicrobial prophylaxis 1 h before skin incision. Skin preparation with chlorexidine-alcohol prevents/decreases surgical site infection.	/ /	Na/High Na/Moderate	Strong
12. Standard anesthetic protocol	To attenuate the surgical stress response, intraoperative maintenance of adequate hemodynamic control, central and peripheral oxygenation, muscle relaxation, depth of anesthesia, and appropriate analgesia is recommended. Fast acting agents?	/	Na/Moderate	Strong
13. Perioperative fluid management	Fluid balance should be optimized by targeting cardiac output using the esophageal Doppler system or other systems for this purpose and avoiding overhydration. Judicious use of vasopressors is recommended with arterial hypotension.	High-risk patients need close and individualized goal directed fluid management. There are several ways to achieve this and all must be used together with sound clinical judgment	Low/High	Strong
14. Preventing intraoperative hypothermia	Normal body temperature should be maintained per-and postoperatively.	Especially relevant for cystectomy patients since operative duration is prolonged	Na/high	Strong
15. Nasogastric intubation	Postoperative nasogastric intubation should not be used routinely	Early removal is recommended	Low/High	Strong
16. Urinary drainage	Transurethral catheter can be removed on postoperative day 1 after pelvic surgery in patients with a low risk of urinary retention	Ureteral stents and transurethral neo-bladder catheter should be used. The optimal duration of ureteral stenting (at least until POD 5) and transurethral catheterization is unknown.	Very low/Low	Weak
17. Prevention of postoperative ileus	A multimodal approach to optimize gut function should involve gum chewing and oral magnesium	/	Moderate/Moderate	Strong
18. Prevention of PONV		Multimodal prophylaxis		Strong

(*continued on next page*)

Table 1 (*continued*)

ERAS single item	Summary	Specifics for cystectomy patients/ open questions	Evidence for cystectomy/ rectal surgery	Grade of recommendation
	A multimodal PONV prophylaxis should be adopted in all patients with ≥2 risk factors.		Very low/Low (High in high-risk patients)	
19. Postoperative analgesia	A multimodal postoperative analgesia should include thoracic epidural analgesia	/	Na/High	Strong
20. Early mobilization	Early mobilization should be encouraged	2 h out of bed POD 0 6 h out of bed POD 1	Na/Low	Strong
21. Early oral diet	Early oral nutrition should be started 4 h after surgery	/	Na/Moderate	Strong
22. Audit	All patients should be audited for protocol compliance and outcomes	Routine audit of outcomes, cost-effectiveness, compliance and changes in protocol	Na/Low	Strong

Na: not available.
ERAS: enhanced recovery after surgery.
LMWH: low molecular weight heparin.
PONV: postoperative nausea and vomiting.
POD: postoperative day.

Preoperative malnutrition requires special attention. Up to 33% of urology patients undergoing surgery are at nutritional risk.[13] For cystectomy patients, preoperative malnutrition independently increases the mortality rate[14]; its impact on morbidity has not been studied. While preoperative oral nutritional support, and especially immunonutrition, is clearly indicated for patients undergoing major gastrointestinal procedures,[15] its role in reducing morbidity and mortality in urology remains unknown.

3. Oral mechanical bowel preparation

Two studies totaling 148 patients assessed the need for bowel preparation before cystectomy. By prospectively including 32 patients undergoing radical cystectomy and ileal conduit diversion without bowel prep, Tabibi et al. found no difference in morbidity or LOS when compared to 30 patients that had undergone standard 3 day mechanical bowel prep.[16] Likewise, Xu et al. found no statistical difference in morbidity, LOS or time to first bowel movement by randomizing 86 patients.[17]

4. Preoperative carbohydrate loading

While there is no study evaluating carbohydrate loading in cystectomy patients, it has been shown that such preoperative loading decreases thirst, insulin resistance and helps maintaining lean body mass and muscle strength in colorectal surgery.[6] The effect of carbohydrate loading in diabetic patients is safe although it remains to be studied the impact on glycemic control on outcome.

5. Preoperative fasting

For decades, patients undergoing surgery necessitating general anesthesia were not allowed per os solids or liquids after midnight, by fear of pulmonary aspiration. This dogma has been challenged and solid food intake up to 6 h and liquids up to 2 h before induction is recommended by European guidelines[18] before surgery.

6. Preanesthesia medications

Surgical removal of the bladder and urinary diversion causes anxiety, especially when a stoma is indicated.[19] While information and counseling decreases anxiety, pharmacological intervention with anxiolytics can be indicated before surgery. ERAS protocols

High quality:
Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality:
Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality:
Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality:
Any estimate of effect is very uncertain

Fig. 1. The GRADE approach to assess the quality of evidence. This approach allows for a clear separation between quality of evidence and strength of recommendations. When the desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not, the study group members offer strong recommendations. On the other hand, when the tradeoffs are less certain, either because of low quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced, weak recommendations become mandatory. Since values and preferences are also taken into account, strong recommendations may, in some cases, be reached from low quality data and vice versa. For items for which no evidence specific to cystectomy was available, the study group decided if the best available evidence from colorectal guidelines could be extrapolated and applied to cystectomy patients.

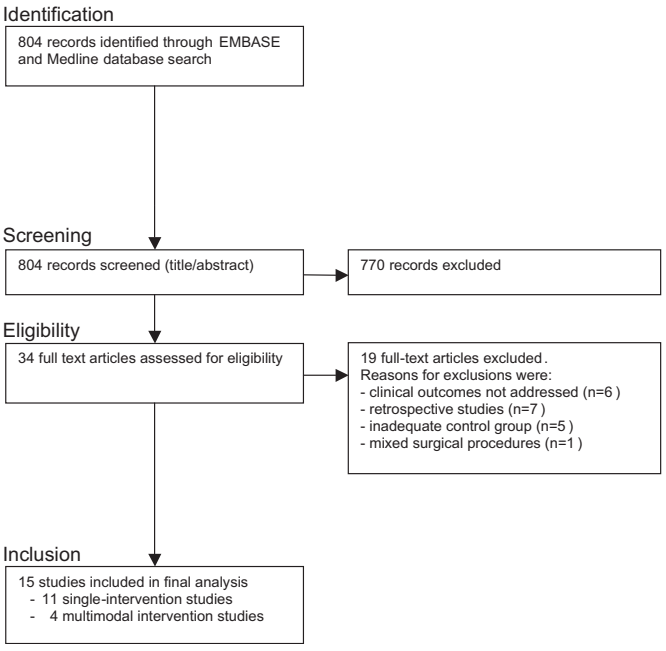

Fig. 2. Selection process according to the PRISMA statement.

Table 2
Summary of studies included for assessment of ERAS for radical cystectomy.

Author	Year	Design	Jadad	Nb of patients (exp/co)	LE	Studied item(s)	Intervention	Morbidity	LOS	Time to bowel transit
Pillai	2011	RCT	2	32/34	1b	Perioperative fluid management	Doppler-guided fluid administration	Decreased	No difference	Decreased
Taylor	2004	Prospective	NA	8/8	2b	Minimally invasive approach	Hand-assisted laparoscopy	No difference	No difference	Decreased
Mattei	2007	RCT	1	25/29	1b	Early removal of urinary drainage	Stents removed directly after uretero-ileal anastomosis	No difference	Not assessed	Increased
Galich	2006	Prospective	NA	13/24	2b	Minimally invasive approach	Robotic cystectomy with extracorporal reconstruction	No difference	Decreased	Not assessed
Porpiglia	2007	Prospective	NA	20/22	2b	Minimally invasive approach	Laparoscopy with extracorporal reconstruction	No difference	No difference	Decreased
Tabibi	2007	Prospective	NA	32/30	2b	No bowel preparation	Versus standard 3 day mechanical bowel prep	Decreased	Decreased	Not assessed
Xu	2010	RCT	1	39/47	1b	No bowel preparation	Versus oral sodium phosphosoda + erythromycin + metronidazole	Decreased	Decreased	Decreased
Adamakis	2011	RCT	2	22/21	1b	Early nasogastric tube removal	Versus removal after first flatus	Decreased	Decreased	Decreased
Lightfoot	2007	RCT	5	11/11	1b	Stimulation of gut motility	Erythromycin	No difference	No difference	No difference
Kouba	2007	Prospective	NA	51/51	2b	Stimulation of gut motility	Chewing gum	No difference	No difference	Decreased
Choi	2010	RCT	3	28/30	1b	Stimulation of gut motility	Chewing gum	No difference	No difference	Decreased
Arumainayagam	2008	Retro	NA	56/56	3	3,5,8,10,18,20,21	Refer to main text for detailed interventions	No difference	Decreased	No difference
Pruthi	2010	Pro/retro	NA	100/262	3	1,7–9,11,15,17–21	Refer to main text for detailed interventions	NA	NA	NA
Brodner	2001	Pro	NA	15/15	2b	8,15,20,21	Refer to main text for detailed interventions	No difference	No difference	Decreased
Donat	1999	Pro	NA	27/54	2b	15,18	Refer to main text for detailed interventions	No difference	No difference	Decreased

suggest avoiding long-acting sedation to enhance postoperative recovery and mobilization.[6] Moreover, long-acting benzodiazepines are associated with cognitive impairment in the elderly. Short acting drugs can be administered safely and can facilitate patient positioning and epidural catether placement. This particular point has not been studied in urological procedures.

7. Thrombo-embolic prophylaxis

The incidence of clinically significant deep vein thrombosis after cystectomy is estimated at 5%.[20] Therefore, as for all major pelvic surgeries, thromboprophylaxis using low molecular weight or unfragmented heparine, which reduces the risk of symptomatic thrombosis, should be used. The addition of compressive stockings and intermittent pneumatic compression devices can further decrease the risk.[6]

There is a high level of evidence that prolonged thromboprophylaxis for up to 4 weeks after oncological pelvic surgery significantly decreases the incidence of symptomatic deep vein thrombosis, when compared to in-hospital prophylaxis,[21] without increasing the risk of bleeding complications.

3.2. Intraoperative items

8. Epidural analgesia (EDA)

No prospective single-intervention study has been conducted to assess the value of EDA in the perioperative management of cystectomy. Thoracic epidurals are however integral part of existing fast-track protocols in urology. Maffezzini et al. reported improved functional outcomes and recommended thoracic EDA at level Th9-11 until the third postoperative day.[22] Another study retrospectively compared 73 patients with EDA vs. 58 patients with patient-controlled morphine-based analgesia after cystectomy.[23] Except for improved pain scores during activity in favor of the EDA group, no significant difference was noted. However, the conclusions of this study are certainly hampered by a small study cohort and a non-randomized patient allocation.

For open colorectal surgery there is overwhelming evidence supporting the use of epidurals in order to dampen the stress response, to provide superior pain relief, to fasten functional recovery, and to reduce cardiopulmonary complications.[6,24] Thoracic insertion around level Th10 is recommended and low doses of either fentanyl or morphine can be added to bupivacaine for pelvic surgeries. Optimal duration of epidurals is supposed to be between 48 and 72 h after surgery. Given the similarities of low rectal and bladder surgery in terms of surgical trauma and postoperative pain, it seems justified to strongly recommend the use of thoracic epidural analgesia for 72 h after cystectomy.

9. Minimally invasive approach

Minimally invasive pelvic surgery has been shown to decrease the inflammatory response when compared to the open approach. Laparoscopic rectal surgery seems to reduce the risk of post-operative ileus, complications and length of stay. However, long term oncological results are awaited before any higher LE statement can be drawn.

Recently, robotic radical cystectomy has been increasingly performed in the setting of bladder cancer treatment and merits special consideration. While open radical cystectomy and pelvic lymph node dissection remains the gold standard in treating non-metastatic muscle invasive bladder cancer,[25] this major surgery is still associated with morbidity as high as 64%.[4] In order to decrease the complication rates, efforts have been made to decrease the

surgical stress by adopting minimally invasive approaches, such as robot-assisted laparoscopic radical cystectomy. Menon et al. were the first to report on the feasibility of robot-assisted radical cystectomy in 2003.[26] Since then, numerous high volume centers have reported their experience with this robotic approach, including a total number of patients over 350.[27] Unfortunately, most of these studies report retrospective data or prospective comparative data, and high quality randomized controlled trials are lacking. Despite these limitations, robot-assisted radical cystectomy seems to be associated with lower overall perioperative complications, longer operative time and shorter LOS, with equivalent short term oncological safety.[27] Future high quality, high volume controlled studies should help in reaching definitive conclusions. In addition, the International Robotic Cystectomy Consortium (IRCC) was created in 2010[28] and has now included over 1000 patients. Based on their latest publication, the 90 days complication rate is 48%, most of them being low grade complications.[29] The number of yielded lymph node and oncological safety seems to be comparable to open radical cystectomy and depend on the surgeon's experience, with 20–30 cases being accepted as the minimal learning curve.[30]

Three prospective case series studies evaluated some form of minimally invasive approach to radical cystectomy. Galich et al. investigated the use of robotic radical cystectomy with extracorporeal urinary diversion in 13 consecutive patients and compared outcomes to an homogenous group of 24 patients undergoing standard open radical cystectomy. They found a lower LOS and reduced blood loss in the robotic group, while operative time was significantly longer. Morbidity and return to bowel function was comparable in both groups. Porpiglia et al. performed 20 laparoscopy-assisted radical cystectomies with extracorporeal urinary diversion and compared postoperative outcome to 22 patients undergoing standard open surgery. They found similar blood loss, operative time and LOS, while the time to oral nutrition and analgesic consumption was significantly reduced in the laparoscopy group. Taylor et al. compared outcomes from 8 hand-assisted laparoscopic cystecomies to 8 open cystectomies. Blood loss, operative time and LOS were similar in both groups. Patients undergoing hand-assisted laparoscopic cystectomy had a quicker return to normal diet and bowel function, while no significant difference in morbidity could be shown. In summary, conflicting results from low quality, underpowered studies exist with regard to minimally invasive radical cystectomy.

10. Resection site drainage

Avoidance of suction-drainage of the peritoneal cavity after colorectal procedures results in comparable anastomotic leak and overall outcomes and can be therefore safely avoided.[6] No study specific to cystectomy is available. Due to the risk of urinary leak, results from colorectal surgery might not apply to cystectomy patients.

11. Antimicrobial prophylaxis and skin preparation

None of the studies selected has investigated whether a specific combination of antibiotics or skin preparation might reduce one of the main ERAS outcomes. Antimicrobial-agents in cystectomy patients should be effective against aerobes and anaerobes. The ideal combination of antibiotics for this purpose remains to be established. However based on the Advisory Statement from the National Surgical Infection Prevention Project, antibiotics should be administered before skin incision and less than 1 h before surgery.[31] Based on the European Association of Urology guidelines, since cystectomy is considered as a "clean-contaminated" surgery, a single perioperative course of a 2nd or 3rd generation cephalosporin is recommended (http://www.uroweb.org/gls/pdf/17_Urological%20infections_LR%20II.pdf).

Regarding the optimal skin preparation, the ERAS recommendations in elective colorectal are of absolute value in cystectomy patients.

12. Standard anesthetic protocol

No prospective single-intervention studies are available which assessed the value of a standardized anesthetic protocol for cystectomy. Current fast-track protocols in urology include thoracic epidural analgesia (Th9-11), minimizing opioids, short-acting anesthetic agents (remifentanil), and prevention of hypoxia and hypothermia; furthermore, blood loss is limited by controlled hypotension (80 mmHg), antifibrinolytics, and timely substitution of blood loss (>500 ml of estimated blood loss) aim to maintain normovolemia and adequate oxygen supply.[22] This practice is very much in line with the recent recommendations for colon and rectal surgery.[6,10] There is thus a strong recommendation for prevention of hypothermia, hypoxemia and hypovolemia although level of evidence for cystectomy patients is absent. The use of epidurals is strongly recommended for benefits mentioned beforehand. When epidural is not feasible intravenous lidocaine infusion can be administered because of its-inflammatory and opioid-sparing properties.[6,10]

Attention should be paid to maintain normoglycemia (possibly blood sugar less than 10 mmol/l), and adequate lung ventilation with low tidal volumes to limit peak airway pressure thus reducing the risk of barotrauma.

13. Perioperative fluid management

Both fluid excess or hypovolemia can provoke splanchnic hypoperfusion, which can then result in ileus, increased morbidity and LOS.[32] While goal directed fluid therapy (GDFT) using esophageal Doppler to achieve "near maximal stroke volume" has been recommended in rectal surgery,[6] these protocols have often been compared to obsolete regimens with either fluid overload or unwarranted restriction. Furthermore, Doppler guidance only reveals whether an increase in fluid administration result in improved cardiac output and not whether there is a clinically significant hypoperfusion in need of correction. Available data deal almost exclusively with ASA I and II patients[33–35] and data for high-risk patients are – as always – wanting. This reduces the external validity of the trial findings as the fittest patients probably have wide safety margins and will cope well with several approaches to fluid management. Importantly, they are probably not in need of any optimization at all. One large trial in colorectal surgery compared GDFT to individualized and best available fluid care in a regimen coined "zero-balance" but this was in fact also goal directed as changes in CVP, heart rate and arterial pressure were used to guide fluid administration.[33] Similarly, the target for therapy in the laparoscopic subgroup was changed from volume response to maintenance of a measured stroke volume.[33] Compared to colorectal surgery, fluid monitoring in cystectomy patients is more challenging as urine output can be unreliable. One RCT investigated GDFT in radical cystectomy patients and concluded with a reduced incidence of ileus and of nausea and vomiting at 24 and 48 h.[34] The caveats noted above also affect this trial. In summary, it appears prudent to assume that ASA III and IV patients need a dedicated, individualized goal directed fluid management run by an experienced anesthetist to ensure adequate tissue perfusion. A Doppler-guided strategy may prove a valuable adjunct in these cases.

14. Preventing intraoperative hypothermia

Prolonged exposure of the abdominal cavity and anesthesia can cause perioperative hypothermia (<36 °C). It has been demonstrated

that hypothermic patients have higher rates of postoperative complications in colonic surgery.[10] Body temperature monitoring has not been investigated as a single ERAS intervention in any of the studies selected. Given the similar physiopathology resulting in impaired thermoregulation in colorectal and cystectomy procedures, maintaining normothermia is strongly warranted.

3.3. Postoperative items

15. Nasogastric intubation

Adamakis et al. conducted an RCT including 43 patients undergoing radical cystectomy and compared early removal of NGT with standard care pathway comprising removal of NGT after first flatus. No difference in morbidity, LOS and recovery of bowel transit was found in the two groups. A Cochrane meta-analysis including 33 RCTs investigating patients undergoing major abdominal surgery showed more postoperative complications and no advantage when prophylactic NGT was maintained after surgery.[37] Routine prolongation of nasogastric intubation after cystectomy is not warranted.

16. Urinary drainage

While there is a low LE that transurethral bladder catheter may be safely removed on postoperative day 1 after pelvic surgery in patients with a low risk of urinary retention,[6] there is no study evaluating the need or the duration of transurethral catheterization after cystectomy and orthotopic bladder reconstruction.

Mattei et al. randomized 37 orthotopic ileal bladder substitute and 17 ileal conduit patients into two groups. Patients in group 1 ($n = 29$) had their ureteral stents removed between day 5–10, while patients in group 2 ($n = 25$) had the stents removed directly after completion of the uretero-ileal anastomosis. Stenting resulted in improved drainage of the upper urinary tract, improved bowel recovery and reduced occurrence of metabolic acidosis. The optimal duration of ureteral stenting has not been investigated.

17. Prevention of postoperative ileus

Specific treatments to prevent postoperative ileus were evaluated in four RCTs and two prospective controlled case series. Three studies related to fluid monitoring (Pillai 2011), laparoscopy-assisted approach (Propiglia 2007) and stenting (Mattei 2007) are described elsewhere with respect to recovery of bowel function. One RCT addressing the use of erythromycin did not show any advantage in the intervention group (Lightfoot 2007). A total of 162 patients undergoing cystectomy were included in two trials to assess the effect of chewing gum (Choi 2011, Kouba 2007). In both trials the intervention group had shorter time to flatus and first bowel movement compared to control group. Both studies failed to show any difference in postoperative morbidity and LOS.

18. Prevention of postoperative nausea and vomiting (PONV)

Non-smokers, female patients, patients with a history of motion sickness and patients using opioids are at high-risk for PONV. In addition, inhalational anesthetics, nitrous oxide and opioids contribute to PONV. In these patients, there is a high level of evidence that a multimodal anti-emetic prophylaxis should be adopted. Two RCTs evaluated the effects of interventions aiming to prevent nausea and vomiting. Pillai et al. showed that intraoperative fluid optimization by esophageal Doppler monitoring of cardiovascular volumes significantly decreased nausea and vomiting at 24 and 48 h. Reduced morbidity and early recovery of bowel transit were observed in the intervention group; LOS was similar.[34] Stenting of the uretero-ileal anastomosis was effective in the prevention of PONV as demonstrated by Mattei et al.[38]

19. Postoperative analgesia (for epidural analgesia, refer to #8)

Multimodal opioid-sparing analgesia is suggested to reduce postoperative ileus and enhance bowel recovery.[10] At least for open abdominal and pelvic surgeries, thoracic epidural analgesia for 48–72 h after surgery can be considered backbone of these strategies for superior pain relief but also for the additional benefits of reduced stress response and reduction of cardiopulmonary complications. Alternatives especially for minimal-invasive procedures are intrathecal analgesia, intravenous lildocaine, locoregional blocks (tranversus abdominis plane (TAP)), and continuous infusion of local anesthetics via pre-peritoneal wound catheters.[39,40] However, comparison of these techniques with epidural analgesia in the context of ERAS remains very limited so far. Additionally, acetaminophen and NSAIDs are recommended for baseline treatment. The latter have recently been put in question though for reports on increased anastomotic leaks. The value of adjunct medications such as gabapentin needs yet to be proven.

For cystectomy procedures, no prospective data are available to add to the body of evidence. However, limited data from studies excluded from the present analysis suggest that the opioid-sparing multimodal pain concepts can probably safely be adopted in major urology surgery.[22,23]

20. Early mobilization

Enhancement of postoperative mobilization has not been specifically studied in any of the trials. Likewise there is no RCT suggesting direct association between early mobilization and improved ERAS outcomes either in colonic or rectal surgery. Nevertheless it is established that prolonged bed rest increases postoperative thromboembolism risk and pulmonary complications. Encouraging early mobilization after surgery should be part of an ERAS protocol in cystectomy.

21. Early oral diet

None of the studies considered has investigated the direct association of early oral or enteral feeding with one of the ERAS outcomes. Normal food intake is considered essential in an ERAS protocol to maintain body homeostasis. Similar outcome has been shown for early enteral nutrition (<24 h) compared to historical standard of care in colorectal surgery. However, no difference in morbidity and particularly in anastomotic leak/dehiscence rate was found in the two groups.[6] Normal diet as opposed to parenteral nutrition should be encouraged and reestablished as soon as possible since no evidence supports routine prolonged fasting after cystectomy.

22. Audit

Audit and feedback generally leads to small but potentially important quality improvements in healthcare. The relative effectiveness of audit and feedback is likely to be greater when baseline adherence to recommended practice is low.[41] Since compliance with ERAS protocols in large studies reporting on colorectal surgery is generally about 60%, auditing compliance is a key factor for successful ERAS protocol implementation.[42] The four main roles of auditing are: 1) measuring clinical outcomes (morbidity, LOS, …); 2) measuring non-clinical outcomes (cost-effectiveness, patient's satisfaction); 3) measuring compliance to ERAS protocols and 4) maintaining the concept as dynamic as possible (including new available evidence and modify the multimodal concept).

4. Conclusions

The present systematic review highlights the paucity in studies addressing enhanced recovery pathways for cystectomy patients, while they are considered standard care for colorectal surgery. Clearly, more data is needed to prove the efficacy of ERAS when applied to major urological procedures. The fact that only 15 studies could be included and that only 7 out of 22 ERAS items were addressed represents a limitation of this study. However, the data presented above indicates a need for a comprehensive protocol based on the best available evidence, extrapolating certain items from other ERAS guidelines including colorectal guidelines. Despite extrapolated data from pelvic surgery, many unanswered questions remains, notably the usefulness of peritoneal cavity and pelvic drainage, the duration of urinary drainage (neo-bladder and ureteral stenting) and the type, timing, route and duration of perioperative nutritional support. While it will be impossible and unnecessary to evaluate each single ERAS items in large volume RCTs, the proposed comprehensive ERAS pathway will allow for future multicentre collaborations evaluating prospective cohorts of urological patients following identical standardized care pathways.

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Author contribution

All authors have equally contributed to the study design and final study inclusion. The authors take equal responsibility for guaranteeing the work.

Conflict of interest

None.

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