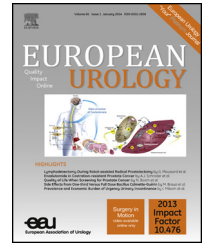




European Association of Urology



Platinum Opinion

Enhanced Recovery After Surgery: Are We Ready, and Can We Afford Not to Implement These Pathways for Patients Undergoing Radical Cystectomy?

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Despite anesthetic and surgical improvements in recent decades, postoperative morbidity remains a common drawback of major surgery. One of the main pathogenic factors leading to morbidity is the surgical stress response. A better understanding of this cascade mediated by the central nervous system, resulting in a systemic release of stress hormones and inflammatory mediators, has led to the development of care pathways attempting to reduce this response. Although no single element can eliminate postoperative morbidity and mortality, a combination of changes could likely reduce postoperative morbidity and lower hospital costs. The concept of a fast track recovery was introduced in the 1990s. It was found that applying evidence-based perioperative principles to patients undergoing open colonic surgery could halve the rate of postoperative complications and shorten the length of stay (LOS) in the hospital [1].

This multimodal perioperative care pathway has evolved into *enhanced recovery after surgery* (ERAS). The initial changes have been complemented by a multitude of measures with proven or probable impact on the surgical stress response. Current ERAS protocols include >20 elements (Fig. 1) and reduce both morbidity and LOS [1]. To assist the transfer from colonic surgery, members of the

ERAS Society who perform radical cystectomy undertook a systematic review of the evidence for ERAS in this field [2]. We highlighted a paucity of high-quality evidence within this field and now wish to encourage clinicians to report their own findings and to undertake high-quality trials of ERAS items for this procedure.

Radical cystectomy represents a significant surgical challenge to patients [3]. Despite the standardization of surgical technique, the introduction of robotic laparoscopic assistance [4], and improved anesthesia and perioperative care protocols, the morbidity after radical cystectomy (with bilateral pelvic lymph node dissection and urinary diversion or bladder reconstruction) is between 30% and 64%, even in high-volume centers [5,6]. Cystectomy patients are mostly elderly and comorbid (many with smoking-related cardiovascular and pulmonary diseases). They are therefore ideal candidates for an ERAS pathway that reduces surgical stress and complications. However, an uncritical application of the guidelines issued from colorectal surgery [7] seems inappropriate because the surgical procedure (small bowel anastomosis, urine within the peritoneal cavity, both extra- and intraperitoneal access) and morbidity of the patients differs between these cohorts.

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ERAS Item	Summary	Specifics for Radical Cystectomy patients	Evidence for Cystectomy / Rectal surgery	Recommendation grade
1. Preoperative counseling and education	Patients should receive 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 alcohol reduction 4 weeks prior to surgery Encouraging physical exercise	NA / Moderate NA / High NA / Moderate	Strong Strong Strong
3. Oral mechanical bowel preparation	Preoperative bowel preparation can be safely omitted		NA / Very low Moderate / High	Strong Strong
4. Preoperative carbohydrate loading	Preoperative oral carbohydrate loading should be administered to all non-diabetic patients		NA / Low	Strong
5. Preoperative fasting	Clear fluid intake until 2hrs and solids food until 6hrs before general anesthesia.		NA / Moderate	Strong
6. Preanesthesia 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. Leave 12h interval between injections and epidural manipulation. LMWH Extended prophylaxis for 4 weeks should be carried out in patients at risk	Cystectomy patients are considered at high risk. Prolonged prophylaxis should therefore be administered.	NA / High NA / High	Strong Strong
8. Epidural analgesia	Thoracic epidural analgesia is superior to systemic opioids in relieving pain. It should be continued for 72h		NA / High	Strong
9. Minimally invasive approach	Try to use in a trial setting. Long term oncological results awaited.	Laparoscopic/robotic cystectomy is recommended inside 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 1h before skin incision. Skin preparation with chlorexidine- alcohol prevents / decreases surgical site infection.		NA / High NA / Moderate	Strong 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.		NA / Moderate	Strong
13. Perioperative fluid management	Fluid balance should be optimized by targeting cardiac output using the esophageal Doppler system. Avoid overhydration. Judicious use of vasopressors is recommended with arterial hypotension.		Low / Moderate	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	Post-operative nasogastric intubation should not be used routinely	Early removal or no NGT is recommended	Low / High	Strong
16. Urinary drainage	Transurethral catheter is removed as early as possible 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	No transurethral catheter if ileal Conduit Multimodal approach to optimize gut function. Involve gum chewing and oral magnesium		Very low / Low Moderate / Moderate	Strong Strong
18. Prevention of PONV	Multimodal PONV prophylaxis in all patients with ≥ 2 risk factors.	Multimodal prophylaxis	Very low / Low (High in high risk patients) NA / High	Strong Strong
19. Postoperative analgesia	Multimodal postoperative analgesia, include thoracic epidural analgesia		NA / High	Strong
20. Early mobilization	Early mobilization should be encouraged	2hrs out of bed same day of surgery (POD 0). 6hrs out of bed POD 1	NA / Low	Strong
21. Early oral diet	Oral nutrition started 4 hrs after surgery		NA / Moderate	Strong
22. Audit	All patients should be audited for compliance and outcomes	Audit outcomes, cost effectiveness, compliance and protocol changes	NA / Low	Strong

Abbreviations

NA: Not applicable (missing). LMWH: Low molecular weight heparin. POD: Post-operative day. NGT: Nasogastric tube. PONV: post-operative nausea and vomiting

Fig. 1 – Enhanced recovery after surgery (ERAS) elements applied to radical cystectomy. Reproduced with permission from the ERAS Society, *Clinical Nutrition, and e-SPEN* [2].

The successful use of modified ERAS protocols has been reported for radical cystectomy. For example, Maffezzini et al. applied 6 of 22 ERAS items (no oral mechanical bowel preparation, epidural analgesia, antimicrobial prophylaxis,

standard anesthetic protocol, preventing intraoperative hypothermia, and early nasogastric tube removal) to 71 patients undergoing radical cystectomy. When compared with historical controls, patients with ERAS had a reduced

time to diet (average from 7 d to 4 d) and shorter LOS (from 22 d to 15 d) without worsening morbidity [8].

Arumainayagam et al. compared 56 consecutive patients undergoing open radical cystectomy with standard perioperative care with 56 patients after implementation of ERAS (including 7 of 22 items: no bowel preparation, no preoperative fasting, epidural analgesia, postoperative nausea and vomiting [PONV] prophylaxis, early oral nutrition, early mobilization, and early removal of abdominal drain [9]). Morbidity and time to first bowel movement was similar in the two groups, but LOS was significantly reduced (from 17 d to 13 d) in the enhanced recovery group.

Pruthi et al. reported the implementation of ERAS after cystectomy (9 of 22 items: preoperative information, deep vein thrombosis prophylaxis, antibiotics prophylaxis, early removal of nasogastric tube, early oral nutrition, early mobilization, prevention of PONV, prevention of ileus, and postoperative analgesia) in 262 patients [10]. When compared with historical controls, the most recent 100 patients had better postoperative recoveries.

Donat et al. combined early nasogastric tube removal with metoclopramide in 27 patients compared with 54 controls. Complication and LOS rates were similar in both groups, but the intervention group had an earlier return to bowel sounds and tolerance of diet [11]. By combining thoracic epidural analgesia, early nasogastric tube removal, early oral nutrition, and mobilization in 15 prospective patients, Brodner et al. showed a reduction of the time to first defecation, with no difference with regard to morbidity or LOS when compared with 15 patients undergoing a standard care plan [12].

Several components of ERAS are critical during surgery. One example is intraoperative fluid replacement (type, timing, and volume) during major surgery. Although some authors advocate standardized restricted fluid replacement, others propose goal-directed regimens. Meta-analysis of Doppler-guided intraoperative fluid management suggests this latter approach produces fewer postoperative complications and shorter LOS than others [13]. As such, ERAS guidelines advocate intraoperative normovolemia and intraoperative fluid therapy based on pulsus paradoxus for abdominal surgery in high-risk patients [7]. This consensus was recently supported by data from radical cystectomy [14]. This randomized controlled trial (RCT) revealed that low intraoperative fluid regimens were associated with lower transfusion and fluid replacement requirements, and subsequently better clinical outcomes.

ERAS pathways clearly improve patient care, reduce morbidity, and shorten LOS. All studies evaluating elements of the ERAS care pathways in radical cystectomy have found benefits in postoperative morbidity, return to bowel function, or LOS. However, none have applied a full ERAS protocol (of the 22 items) to radical cystectomy patients. Thus the benefits of a full ERAS pathway remain unknown. Although the body of evidence for the use of ERAS protocols in cystectomy patients is increasing rapidly, drawbacks remain. For instance, most studies are of limited quality and are either underpowered or retrospective. Some surgeons

have criticized the initial results of ERAS RCTs, arguing that the improved outcome was mainly due to the so-called Hawthorne effect [15]. It is therefore mandatory to measure clinical outcomes in a standardized manner to provide the highest and most reliable evidence. Also, compliance with the protocols is important and requires an initial increased workload at implementation (which might be considered a drawback). Finally, there is a need for standardization and adaptation of protocols tailored to the surgical specifics of the respective specialty. Such protocols are not yet widely available. Prospective auditing is more likely to prove efficiency than more randomized trials, which might be considered unethical today. Because they are highly complex and impossible to blind against, ERAS protocols are not particularly well suited for randomized designs, although it is possible [16].

Multicenter prospective studies using a centralized database will help answer questions such as the optimal perioperative nutritional support; the need, type, and duration of pelvic and urinary catheterization; and the real benefits of full ERAS protocols on morbidity, mortality, LOS, readmission rate, and costs. The ERAS Society has created a group focused on developing ERAS for major urologic procedures, starting with radical cystectomy. A review of the literature and the evidence forming a basis for a protocol has been assembled [1] and is available online (www.erassociety.org). In line with the previous work produced by the society, this guideline will be tested in a multicenter evaluation. We now welcome interested urologists to join and help further these developments for our patients.

Conflicts of interest: The authors have nothing to disclose.

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