Enhanced recovery after surgery - ERAS, a new multimodal approach in radical cystectomy patients

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Abstract

Enhanced recovery after surgery (ERAS) represents a concept first introduced over two decades ago. This concept comprises of a multitude of pre, intra and post operatory measures that have a primordial goal in reducing stress induced by surgery, and starting early mobilization and nutrition for the patient.

ERAS protocols were first implemented in colorectal surgery where now studies show level 1 evidence in lowering complication rates and shortening hospital stay. Comparing radical cystectomy with colorectal surgery, several differences that harden the usefulness of ERAS in urologic surgery appear.

As in colorectal surgery the ERAS society recommendations for cystectomy patients divide the possible applicable pathways in pre, intra and post operatory items.

Even though some elements appear at first glance practically impossible to put into practice for cystectomy patients, as resection site drainage and urinary drainage due to certain morbidity escalation, most of the program’s pathways look encouraging and logical due to confirmation studies in colorectal surgery. ERAS protocols represent a new approach in modern urologic surgery. They are based on hard scientific evidence proved in large prospective clinical trials of colorectal surgery and also urologic surgery. Centers and physicians are encouraged to implement this pathway for the better management of patients resulting in a faster recovery, shorter hospital stay, lower costs and improved quality of life, while maintaining an optimal oncologic control.

Keywords: ERAS, radical cystectomy, minimally invasive approach, early mobilization, early nutrition, epidural analgesia

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Enhanced recovery after surgery (ERAS) represents a concept first introduced over two decades ago. Radical cystectomy for patients with muscle invasive bladder cancer (MIBC) represents a form of major surgery. Major surgery usually relates to early and late morbidity as cardio-pulmonary, infectious and gastrointestinal complications that induce long hospital stay and patient rehabilitation. This concept of surgery represents a multitude of factors composed of pre, intra and post operative measures that have a primordial goal in reducing stress induced by surgery, and starting early mobilization and nutrition for the patient. Kehlet was the first to show that all these factors combined determine an enhanced recovery with a shorter hospital stay, lower morbidity and complication rates [1].

Bladder cancer is a disease characterized by recurrence and progression, 57% of patients treated through radical cystectomy have muscle invasion at presentation, while 43% progress to muscle invasive carcinoma [2,3].

The guidelines state that about one third of MIBC patients have undetected metastases at the time of treatment of the primary tumor and 25% of patients have lymph node involvement at the time of radical cystectomy [2,4].

In an attempt to reduce recurrence and progression and improve survival some authors indicate immediate radical cystectomy for T1G3 associated with concurrent bladder CIS, multiple and/or large T1G3 and/or recurrent T1G3, T1G3 with CIS in the prostatic urethra, unusual histology of urothelial carcinoma and lymph-vascular invasion [2,5].

The fact is that patients that undergo radical cystectomy at the time of non-muscle invasive disease have a disease free survival rate at 5 years of 80%, explaining the fact that early surgery improves survival [2,6-11]. This being said, surgery comes at a price, radical cystectomy having a high early complication rate (first 90 days after surgery), large recent studies going up to almost 60% of cases [12].

ERAS protocols were first implemented in colorectal surgery where now studies show level 1 evidence in lowering complication rates and shortening hospital stay [13].

Comparing radical cystectomy with colorectal surgery, several differences that harden the usefulness of ERAS in urologic surgery appear: longer operating time, small bowel anastomosis, larger dissection area, extended or supra-extended pelvic lymphnode dissection, greater blood loss, urine leak in the peritoneal and pelvic cavities, intra and extraperitoneal access and dissection [14].

Recently some authors have managed to establish a thorough systematic review of the appliance of ERAS pathways in cystectomy patients [14].

As in colorectal surgery the ERAS society recommendations for cystectomy patients divide the possible applicable pathways in pre, intra and post operative items, (see Table No.1 from Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS!) society recommendations) [14].

Even though some elements appear at first glance practically impossible to put in practice for cystectomy patients, as resection site drainage and urinary drainage, due to certain morbidity escalation, most of the program’s pathways look encouraging and logical due to confirmation studies in colorectal surgery.

For example the pre-operative measures as preoperative counseling and education, preoperative medical optimization, oral mechanical bowel preparation, preoperative carbohydrates loading, preoperative fasting, preanaesthesia medication, thrombosis prophylaxis and epidural analgesia define a well documented setting which encourage program implementation [14].

The oral mechanical bowel preparation can be safely omitted as Xu R. et al. show in a recent study that no advantage is gained by adopting this measure [14, 15].

Regarding preoperative fasting and carbohydrate loading the guidelines from the European Society of Anaesthesiology recommend that adults and children should be encouraged to drink clear fluids (water, pulp-free juice, tea) up to 2 hours before elective surgery and solid food should be prohibited for 6 hours before surgery for the reason that prolonged fasting is an improper preoperative strategy that doesn’t reduce the stress of surgery [16].

Epidural analgesia represents one of the most important key points of the ERAS protocol, society guidelines mentioning two recent important studies regarding cystectomy patients [17,18].

Mafezzini M et al recommend analgesia at the point of epidural thoracic cannula T9-T11 [17]. Another study by Torren P. et al clearly proves that patient controlled epidural analgesia for radical cystectomy cases results in less immediate postoperative pain, the patients progressing to early alimentation [18].

Intra-operative measures are represented by: minimally invasive approach, resection site drainage, antimicrobial prophylaxis and skin preparation, standard anesthetic protocol, perioperative fluid management, prevention of intraoperative hypothermia.
**ERAS pathways for radical cystectomy patients**

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**Table 1**

<table>
<thead>
<tr>
<th>ERAS single item</th>
<th>Summary</th>
<th>Specifics for cystectomy patients/rectal surgery</th>
<th>Evidence for cystectomy/rectal surgery</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Preoperative counseling and education</td>
<td>Patients should receive routine dedicated preoperative counseling and education.</td>
<td>Surgical details, hospital stay and discharge criteria in oral and written form; anaesthesia; patient's expectations</td>
<td>Naive</td>
<td>Strong</td>
</tr>
<tr>
<td>2. Preoperative medical preparation</td>
<td>Preoperative optimization of medical conditions should be recommended. Preoperative nutritional support should be considered, especially for malnourished patients.</td>
<td>Correction of anemia and comorbidities nutritional support. Encouraging physical exercise 4 weeks prior to surgery; reduction of alcohol intake.</td>
<td>Naive/Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>3. Oral mechanical bowel preparation</td>
<td>Preoperative bowel preparation can be safely omitted.</td>
<td>/</td>
<td>Naive</td>
<td>Strong</td>
</tr>
<tr>
<td>4. Preoperative carbohydrate loading</td>
<td>Preoperative oral carbohydrate loading should be administered to all non-diabetic patients.</td>
<td>/</td>
<td>Naive</td>
<td>Strong</td>
</tr>
<tr>
<td>5. Preoperative fasting</td>
<td>Intake of clear fluids up until 2 h before induction of general anaesthesia is recommended. Solids are allowed up until 6 h before anaesthesia.</td>
<td>/</td>
<td>Naive/Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>6. Peri-anesthesia medication</td>
<td>Resistance of long-acting narcotics. Patients should receive 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 epidermal manipulations.</td>
<td>Cystectomy patients are considered at risk; extended prophylaxis should therefore be administered.</td>
<td>Naive/Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>7. Thromboembolic prophylaxis</td>
<td>Thoracic epidural analgesia is superior to opioid epidural in reducing pain. It should be continued for 72 h.</td>
<td>/</td>
<td>Naive/High</td>
<td>Strong</td>
</tr>
<tr>
<td>8. Minimally invasive approach</td>
<td>At most feasible in trial setting. Long-term oncological results awaited.</td>
<td>Laparoscopy/robotic cystectomy is not recommended outside a trial setting until long-term results are available.</td>
<td>Low/Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>10. Resection site drainage</td>
<td>Peri-anastomotic and/or pelvic drains can be safely omitted.</td>
<td>Because of urine leak; drainage might be required in cystectomy patients.</td>
<td>Naive</td>
<td>Weak</td>
</tr>
<tr>
<td>11. Antimicrobial prophylaxis and skin preparation</td>
<td>Patient should receive a single dose antimicrobial prophylaxis 1 h before skin incision. Skin preparation with chlorhexidine-alcohol prevents/decreases surgical site infection.</td>
<td>/</td>
<td>Naive</td>
<td>Strong</td>
</tr>
<tr>
<td>12. Standard anesthetic protocol</td>
<td>/</td>
<td>/</td>
<td>Naive/Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>13. Preoperative fluid management</td>
<td>Fluid balance should be optimized by targeting cardiac output using the esophageal Doppler monitor or other systems for this purpose and avoiding overhydration. Justification of use of vasopressors is recommended with arterial hypotension.</td>
<td>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.</td>
<td>Low/Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>14. Preventing intraoperative hypothermia</td>
<td>Normal body temperature should be maintained peri-and postoperatively.</td>
<td>Especially relevant for cystectomy patients since operative duration is prolonged. Early removal is recommended.</td>
<td>Naive/High</td>
<td>Strong</td>
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<tr>
<td>15. Urinary drainage</td>
<td>Transurethral catheter can be removed on postoperative day 1 after pelvic surgery in patients with a low risk of urinary retention.</td>
<td>Urinary stents and transurethral neo-bladder catheter should be used. The optimal duration of vesical stenting (at least until POD 5) and transurethral catheterization is unknown.</td>
<td>Very low/Very low</td>
<td>Weak</td>
</tr>
<tr>
<td>17. Prevention of postoperative ileus</td>
<td>A multimodal approach to optimize gut function should involve gum chewing and oral magnesium.</td>
<td>/</td>
<td>Moderate/Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>18. Prevention of PONV</td>
<td>A multimodal PONV prophylaxis should be adopted in all patients with ≥2 risk factors.</td>
<td>Multimodal prophylaxis</td>
<td>Very low/Low (High in high-risk patients)</td>
<td>Strong</td>
</tr>
<tr>
<td>19. Postoperative analgesia</td>
<td>A multimodal postoperative analgesia should include thoracic epidural analgesia. Early mobilization should be encouraged.</td>
<td>/</td>
<td>Naive</td>
<td>Strong</td>
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<tr>
<td>20. Early mobilization</td>
<td>Early oral diet should be started 4 h after surgery.</td>
<td>2 h out of bed POD 0 6 h out of bed POD 1</td>
<td>Naive</td>
<td>Strong</td>
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<tr>
<td>21. Early oral diet</td>
<td>All patients should be afforded for protocol compliance and outcomes.</td>
<td>Routine audits of outcomes, cost-effectiveness, compliance and changes in protocol</td>
<td>Naive</td>
<td>Strong</td>
</tr>
</tbody>
</table>

**Notes:**
- ERAS: enhanced recovery after surgery.
- LMWH: low molecular weight heparin.
- POD: postoperative day.

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**ERAS society recommendations [14]**
The minimally invasive approach represents a very important element in lowering morbidity and hospital stay. Usually, open transperitoneal radical cystectomy represents the treatment of choice for MIBC patients. EAU guidelines analyzing recent studies show that laparoscopic radical cystectomy (LRC) patients with extracorporeal reconstruction have a significant longer operative time but less blood loss, less analgesic requirement, less time to oral intake and of course a shorter hospital stay in contrast with open radical cystectomy patients who develop more minor complications [2, 19-26].

Another option for MIBC patients is represented by open extraperitoneal radical cystectomy (OERC). Jentzmik F. et al found that the incidence of postoperative ileus is lower after this technique [27]. Another author comparing LRC with OERC finds besides the benefits of LRC as less blood loss, less time to regained bowel function, and hospital stay a shorter operating time [28]. Both groups at the 3 year overall follow-up had no differences regarding cancer-specific or cancer-free survival [28].

Even though appealing, extraperitoneal cystectomy was analyzed in a recent study on 136 patients. Zhu YP. Et al found studying the histologic results of the bladder peritoneum that tumor stage and lymph node status are independent predictors of peritoneal involvement, and he recommends that the technique should be performed only in selected patients with muscle invasive disease pT1-T2. Patients with higher stages should not have the peritoneum covering the bladder preserved.

With this said, OERC represents an inspired technique that should be used in selected patients with muscle confined disease having the benefits of lowering morbidity and overall patient costs compared to LRC with maintaining an excellent oncologic control.

Regarding the rest of intraoperatory measures, resection site drainage represents a barrier that at least for now is impossible to overcome in urologic surgery due to extended pelvic lymph node dissection and urinary tract reconstruction, as for the other measures, the guidelines offer strong scientific material that suggest safe applicability in cystectomy patients.

In what concerns the post-operative pathway elements are: nasogastric intubation, urinary drainage, prevention of postoperative ileus, prevention of postoperative nausea and vomiting, postoperative analgesia, early mobilization, early oral diet and audit. We are going to summarize and discuss the most important keypoints.

As stated, urinary drainage represents a hard to apply element in the setting of cystectomy patients [14].

Regarding nasogastric intubation, most authors recommend catheter suppression right after the end of surgery with encouraging results [14, 29-31].

The prevention of postoperative ileus represents a blend of elements starting with no preoperative fasting, early gastric tube removal, minimally invasive approach to surgery, postoperative analgesia and early mobilization.

Early mobilization in these patients represents a sensitive matter due to increased age in the cystectomy population, not counting advanced stage patients. The guidelines point no studies that indicate the benefit of early mobilization in radical cystectomy patients [14]. In the ERAS setting the urologic patient benefits from carbohydrate loading with no fasting, epidural analgesia with post-operative pain control, minimally invasive approach and other protocol elements that should encourage an early mobilization, even though radical cystectomy represents a debilitating procedure with large dissections in sensitive fragile areas.

ERAS protocols represent a new approach in modern urologic surgery. They are based on hard scientific evidence proved in large prospective clinical trials of colorectal surgery and also urologic surgery. Centers and physicians are encouraged to implement this pathway for the better management of patients resulting in a faster recovery, shorter hospital stay, lower costs and improved quality of life, while maintaining an optimal oncologic control.

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References
5. Brausi M, Olaru V. Management of high-risk non-muscle invasive


