Enhanced Recovery after Radical Cystectomy (ERARc) (aka ERAS)

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### Disclosures

<table>
<thead>
<tr>
<th>Role</th>
<th>Company</th>
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<tbody>
<tr>
<td>Consultant/Speaker</td>
<td>Abbvie, Astellas, Bayer, BioCancell, BioSyent, Ferring, Janssen, Lilly, Merck, Roche, Sanofi, Sitka, Spectrum</td>
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<td>Grant Funding</td>
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<td>Clinical Trials</td>
<td>Roche, Sitka, BioCancell</td>
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Key Learning Objectives

Upon completion of this session, participants should be able to:

• Define the key components of an ERAS protocol
• Review the evidence supporting the use of ERAS for radical cystectomy
• Describe how to implement an ERAS protocol for radical cystectomy at an individual hospital
• Evaluate the role of alvimopan (μ-opioid antagonist) in an ERAS protocol
Which of the following is **not** a recommendation of the ERAS Society for major abdominal/pelvic surgery?

1. Preoperative bowel preparation can be safely omitted
2. Avoid giving any fluids within 6 hours of anesthesia
3. Administer preoperative oral carbohydrate loading to all non-diabetic patients
4. Provide extended thrombosis prophylaxis for 4 weeks in at-risk patients
Key Principles of ERAS

- concept of “fast-track” surgery introduced in the 1990s by Kehlet
- evidence-based, multidisciplinary approach
- standardized perioperative care pathway designed to:
  1. Reduce stress → reduce morbidity
  2. Maintain postop physiologic function → faster recovery
  3. Enhance mobilization → shorter hospital stay

Core ERAS Protocol

- No NG tubes
- Early oral nutrition
- Early removal of catheters/drains
- Stimulation of gut mobility
- Avoidance of salt and water overload
- Prevention of nausea and vomiting
- Non-opioid oral analgesia/NSAIDs
- Early mobilization
- Warm air body heating in theatre
- Active patient involvement at all stages

Preoperative:
- Preadmission counselling
- No/selective bowel-prep
- Fluid and carb loading/no prolonged fasting
- No premed
- Antibiotic prophylaxis
- Thrombo-prophylaxis
- Mid-thoracic epidural anesthesia/analgesia
- Short-acting Anesthetic agent

Intraoperative:
- Avoidance of Sodium/fluid overload
- No drains

Postoperative:
- Audit of compliance/outcomes
- Early mobilization

A Team Approach to ERAS

- multidisciplinary approach involving
  - Surgeons
  - Anesthetists
  - Nurses
  - Physiotherapists
  - Stoma therapists
  - Dieticians
  - Patient and family

- iterative process with regular audits and potential updates → incremental improvements

Kehlet H. Br J Anaesth 1997;78:606-17
Evolution of ERAS

- the ERAS Study Group (which later became the ERAS Society) established the first ERAS protocol in colorectal surgery in 2005

- since then, ERAS protocols have been used for other surgeries:
  - Bariatric surgery
  - Rectal surgery
  - Pancreaticoduodenectomy
  - Radical cystectomy

Rationale for the Use of ERAS Protocols with Rad Cystectomy

- GI complications are a common cause of post-operative morbidity following radical cystectomy\textsuperscript{1}
  - Prolonged hospital stay
  - Increased cost

- ERAS protocols reduce surgical stress and facilitate postop recovery in other specialties (e.g. colorectal, gynecology, etc)\textsuperscript{2,3}

- complications and length of hospital stay not affected by surgical approach (open vs. robotic)\textsuperscript{4,5}
  - perioperative management may have greater impact

“Fast Track” Peri-op Care Plan

Pre-op
• ........

Intra-op
• ........

Post-op
• ........

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

Yannick Cerantola a, Massimo Valerio a, Beata Persson b, Patrice Jichlinski a, Olle Ljungqvist c, Martin Hubner d, Wassim Kassouf e, Stig Muller f, Gabriele Baldini g, Francesco Carli g, Torvind Naesheim h, Lars Ytrebo h, Arthur Revhaug i, Kristoffer Lassen i, Tore Knutsen k, Erling Aarsether k, Peter Wiklund j, Hitendra R.H. Patel k,*
Carbohydrate drink should be given up to what time before surgery?

1. Midnight before surgery
2. 6 hrs before surgery
3. 4 hrs before surgery
4. 2 hrs before surgery
5. Up to induction of general anesthesia

Summary of Responses

- 1: 8%
- 2: 18%
- 3: 23%
- 4: 53%
- 5: 0%
<table>
<thead>
<tr>
<th>ERAS item recommendation</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide routine dedicated <strong>preoperative counseling and education</strong></td>
<td>Strong</td>
</tr>
<tr>
<td><strong>Preoperative optimization of medical conditions</strong> recommended. Consider preoperative nutritional support, especially for malnourished patients</td>
<td>Strong</td>
</tr>
<tr>
<td>Preoperative <strong>bowel preparation can be safely omitted</strong></td>
<td>Strong</td>
</tr>
<tr>
<td>Administer <strong>preoperative oral carbohydrate loading</strong> to all non-diabetic patients</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>Clear fluids</strong> recommended up until 2 h before induction of general anesthesia. Solids allowed up until 6 h before anesthesia</td>
<td>Strong</td>
</tr>
<tr>
<td>Avoid use of long-acting sedatives before anesthesia</td>
<td>Strong</td>
</tr>
<tr>
<td>Well-fitting compression stockings and <strong>thrombosis prophylaxis</strong> with LMWH recommended. Extended prophylaxis for 4 weeks after surgery. 12 h interval between injections and epidural</td>
<td>Strong</td>
</tr>
</tbody>
</table>

LMWH = Low molecular weight heparin

Preoperative Bowel Prep: Evidence in Cystectomy

- 62 patients undergoing urinary diversion\(^1\)
  - 3-day standard bowel prep (n = 30) vs. only soft diet, no oral intake 8 h before surgery (n = 32)
  - Followed for min. 6 mos
  - No difference in morbidity or length of hospital stay

- 86 patients undergoing radical cystectomy and ileal conduit\(^2\)
  - Standard preoperative bowel prep (n = 47) vs. no bowel prep (n = 39)
  - No statistical difference in the frequency of complications or patient recovery

- ERAS Society Recommendation:\(^3\)
  - Preoperative bowel preparation can be safely omitted

Preoperative Nutrition

- Preoperative nutritional deficiency is a strong predictor of 90-day mortality and poor overall survival\(^1\)

- Preoperative carb loading with clear electrolyte/carb liquids: reduces thirst, maintains lean body mass and muscle strength, and decreases recovery time\(^2\)
  - Give up to 2 hours before surgery

- Correction of preoperative nutritional deficiencies may require prolonged parenteral/enteral nutrition\(^3\)

- ERAS Society Recommendation:\(^4\) Preoperative nutritional support should be considered, especially for malnourished patients

Preoperative Fasting and Carbohydrate Loading

- Meta-analysis of 21 randomized studies (major abdominal surgery, lap chole, hernia repair, thyroidectomy and orthopedic surgery)
  - 733 ≥ 50 g oral carbohydrates 2-4 h pre-anaesthesia
  - 952 control (fasted/placebo)

- No difference in LOS between the two groups
  - Subgroup analysis: preop carb before major abdominal surgery = 1 day lower LOS

- No reported aspiration pneumonitis

- No increase in complications

- ERAS Society Recommendation: Preoperative oral carbohydrate loading should be administered to all non-diabetic patients*. Intake of clear fluids up until 2 h before induction of general anesthesia is recommended

*The effect of carbohydrate loading in diabetic patients is safe, although the impact of glycoemic control on outcome remains to be studied

## ERAS Society Recommendations for Cystectomy: Intraop Items

<table>
<thead>
<tr>
<th>ERAS item recommendation</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thoracic epidural analgesia</strong> superior to systemic opioids in relieving pain and should be continued for 72 h</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>Minimally invasive approach</strong> feasible at most; in trial setting</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>Perianastomotic and/or pelvic drain can be safely omitted</strong></td>
<td>Weak</td>
</tr>
<tr>
<td>Give single-dose <strong>antimicrobial prophylaxis</strong> 1 h before skin incision. Skin prep with chlorexidine-alcohol.</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>Standard anesthetic protocol:</strong> Maintain adequate hemodynamic control, central and peripheral oxygenation, muscle relaxation, depth of anesthesia, and appropriate analgesia to attenuate surgical stress response (fast-acting agents)</td>
<td>Strong</td>
</tr>
<tr>
<td>Optimize fluid balance by targeting cardiac output using esophageal Doppler system and avoiding overhydration. Judicious use of vasopressors recommended with arterial hypotension</td>
<td>Strong</td>
</tr>
<tr>
<td>Maintain normal body temperature per- and postoperatively</td>
<td>Strong</td>
</tr>
</tbody>
</table>

## ERAS Society Recommendations for Cystectomy: Postop Items

<table>
<thead>
<tr>
<th>ERAS item recommendation</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postoperative nasogastric intubation</strong> should not be used routinely</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>Transurethral catheter</strong> can be removed on postoperative day 1 after pelvic surgery in patients with a low risk of urinary retention</td>
<td>Weak</td>
</tr>
<tr>
<td>A multimodal approach to optimize gut function and <strong>prevent postoperative ileus</strong> should involve gum chewing and oral magnesuim</td>
<td>Strong</td>
</tr>
<tr>
<td>Adopt <strong>PONV prophylaxis</strong> in all patients with ≥ 2 risk factors*</td>
<td>Strong</td>
</tr>
<tr>
<td>A multimodal <strong>postoperative analgesia</strong> should include thoracic epidural analgesia†</td>
<td>Strong</td>
</tr>
<tr>
<td>Encourage <strong>early mobilization</strong></td>
<td>Strong</td>
</tr>
<tr>
<td>Start <strong>early oral nutrition</strong> 4 h after surgery</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>Audit</strong> all patients for protocol compliance and outcomes</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Example of an ERAS Protocol for Radical Cystectomy

Preoperative
- Preadmission counseling
- Fluid and carbohydrate loading
- No prolonged fasting
- No/selective bowel preparation
- Antibiotic prophylaxis
- Thromboprophylaxis
- No premedication

Intraoperative
- Short-acting anesthesia agents
- Mid-thoracic epidural anesthesia/analgesia
- No drains
- Avoidance of salt and water overload
- Maintenance of normothermia (body warmer/warm intravenous fluids)

Postoperative
- Mid-thoracic epidural anesthesia/analgesia
- No nasogastric tubes
- Prevention of nausea and vomiting
- Avoidance of salt and water overload
- Early removal of catheter
- Early oral nutrition
- Non-opioid oral analgesia/NSAIDs
- Early mobilization
- Stimulation of gut motility
- Audit of compliance and outcomes

NSAIDs = Nonsteroidal anti-inflammatory drugs

ERAS in Radical Cystectomy: Retrospective Feasibility Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-ERAS</th>
<th>Post-ERAS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time</td>
<td>355 mins</td>
<td>349 mins</td>
<td>0.72</td>
</tr>
<tr>
<td>Perioperative bleeding</td>
<td>1,000 mL</td>
<td>1,100 mL</td>
<td>NS</td>
</tr>
<tr>
<td>Time to first passage of stool</td>
<td>5.4 days</td>
<td>3.7 days</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NGT insertion due to POI</td>
<td>12 (31%)</td>
<td>3 (10%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Reoperation</td>
<td>5 (13%)</td>
<td>2 (6%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Total LOS, median days (range)</td>
<td>12 (10-64)</td>
<td>11 (9-107)</td>
<td>0.18</td>
</tr>
<tr>
<td>Adherence to ERAS protocol elements</td>
<td>56%</td>
<td>77%</td>
<td>0.07</td>
</tr>
<tr>
<td>Readmissions</td>
<td>10 (28%)</td>
<td>1 (4%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

NGT = Nasogastric tube
POI = Postoperative paralytic ileus
LOS = Length of stay

Auditing of a Successful ERAS Protocol for Open Radical Cystectomy

- Retrospective review
- ERAS introduced in Jan 2011
  - **ERAS-1**
- Audit in Aug 2012 with multiple changes to achieve “marginal gains”
  - **ERAS-2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-ERAS (n = 69)</th>
<th>ERAS-1 (n = 37)</th>
<th>ERAS-2 (n = 27)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS, days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>14</td>
<td>10</td>
<td>7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean</td>
<td>16.0</td>
<td>12.9</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>Median time to flatus</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>0.08</td>
</tr>
<tr>
<td>Ileus, %</td>
<td>44.9</td>
<td>29.7</td>
<td>14.8</td>
<td>0.017</td>
</tr>
<tr>
<td>Positive nodes, %</td>
<td>10.1</td>
<td>16.2</td>
<td>44.4</td>
<td>0.0046</td>
</tr>
<tr>
<td>Mean node yield</td>
<td>8.4</td>
<td>8.2</td>
<td>16.7</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

LOS = Length of stay

Quality of life impact

ERAS vs. conservative regimen: EORTC QLQ-30 comparison

- 101 patients randomized:
  - ERAS (n = 62)
  - Conservative regimen (n = 39)

- ERAS improved:
  - QOL measures
  - Wound healing disorders (p < 0.006)
  - Fever (p < 0.004)
  - Thrombosis (p < 0.027)
  - Demand for analgesics (p < 0.01)
  - Food consumption vs. food offered (p < 0.02)
  - Time in intermediate care unit (p < 0.001)

<table>
<thead>
<tr>
<th></th>
<th>Day 3</th>
<th>Day 7</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global health status/QOL</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Physical functioning 2</td>
<td>0.011</td>
<td>NS</td>
<td>0.002</td>
</tr>
<tr>
<td>Role functioning 2</td>
<td>NS</td>
<td>0.025</td>
<td>0.016</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>0.015</td>
<td>0.046</td>
<td>0.004</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>NS</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Social functioning</td>
<td>NS</td>
<td>0.049</td>
<td>0.049</td>
</tr>
<tr>
<td>Fatigue</td>
<td>NS</td>
<td>0.014</td>
<td>0.003</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Pain</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>NS</td>
<td>NS</td>
<td>0.033</td>
</tr>
<tr>
<td>Insomnia</td>
<td>NS</td>
<td>NS</td>
<td>0.019</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.046</td>
<td>0.009</td>
<td>0.003</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = Not significant

New Concept: Pre-habilitation Before Radical Cystectomy

- Enhance functional capacity before surgery and enable patient to better withstand and recover from the stress of surgery

- Poor baseline physical performance capacity and nutritional status increase risk of complications after major surgery and prolong recovery
  - Optimizing patient’s functional and metabolic reserve through prehabilitation will likely improve outcomes

- Prehab program must continue in the postoperative period

- Prehab includes:\(^1,^2\)
  - Aerobic and resistance exercises
  - Nutritional counseling and protein supplementation
  - Relaxation exercises

Which of the following statements about alvimopan is **false**?

1. Alvimopan is a peripheral opioid receptor antagonist that reduces the rate of post-op ileus and does not affect pain control.

2. Administration of alvimopan starts with a pre-op dose and continues for 7 days.

3. Use of alvimopan leads to shortened length of hospital stay after radical cystectomy.

4. Administration of alvimopan at the time of post-op ileus has been shown to hasten recovery of bowel function.
Alvimopan: Mechanism of Action

Opioids bind to central μ-opioid receptors in CNS → analgesia

Blood-brain barrier

Continued activation of μ opioid receptors → No reversal of analgesia or opioid withdrawal

Opioids bind to peripheral μ-opioid receptors in GI tract → inhibition of bowel function

Opioid dislodged from μ-opioid receptors in GI tract → No GI effects

RCT: Alvimopan vs. Placebo  
After Radical Cystectomy

<table>
<thead>
<tr>
<th>End point</th>
<th>Alvimopan 12 mg (n = 143)</th>
<th>Placebo (n = 134)</th>
<th>Difference (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to GI-2 recovery, mean days (SE)</td>
<td>5.5 (0.18)</td>
<td>6.8 (0.23)</td>
<td>−1.3 (−1.9 to −0.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Time to discharge, mean days (SE)</td>
<td>6.9 (0.2)</td>
<td>7.8 (0.2)</td>
<td>−0.9 (−1.5 to −0.4)</td>
<td>−</td>
</tr>
<tr>
<td>Postoperative LOS, mean days (SD)</td>
<td>7.44 (3.05)</td>
<td>10.07 (8.23)</td>
<td>−2.63</td>
<td>0.005</td>
</tr>
<tr>
<td>Prolonged LOS (&gt; 7 days), %</td>
<td>32.9 (3.05)</td>
<td>51.5 (8.23)</td>
<td>−18.6</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>POI-related morbidity,%</td>
<td>8.4</td>
<td>29.1</td>
<td>−20.7</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

LOS = Length of stay  
POI = Postoperative ileus

Alvimopan vs. Placebo After Radical Cystectomy: Cost-Effectiveness Analysis

- economic analysis of 277 patients given alvimopan 12 mg or placebo following radical cystectomy

- mean total combined costs decreased by $2,640 per patient for alvimopan vs. placebo (p < 0.068)

- postoperative ileus-related health care costs decreased by US $2,340 alvimopan vs. placebo (p < 0.04)

Shortened Hospital Stay With ERAS After Radical Cystectomy

- n=110 patients
- ERAS protocol included:
  - No preoperative bowel preparation
  - Minimization of perioperative fluid intake
  - Decreased narcotic use
  - Early feeding and mobilization
  - Use of alvimopan/cholinergics/prokinetics
- Median length of stay = 4 days (vs. 8 days in historical matched controls, p < 0.01)
- 82% achieved bowel movement by postoperative day 2

Conclusions

- GI complications are a common cause of postoperative morbidity following radical cystectomy, resulting in prolonged hospital stays and increased costs.

- ERAS protocols have been effectively implemented in radical cystectomy, resulting in shorter LOS, quicker return of bowel function, fewer complications (ie, other non-bowel complications), and cost savings.

- An effective ERAS protocol involves a team approach involving many specialties, as well as the patient.
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