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REVIEW

Enhanced recovery protocol for radical cystectomy: a primer

J Lazarus,[1] J Howlett,[1] M Dewar,[1] AS Salukazana,[1] B Patel,[1] S Bannister,[1] K Timmerman,[2] M Gibbs[2]

[1] *Division of Urology, Groote Schuur Hospital, University of Cape Town, South Africa*
[2] *Department of Anaesthesia and Perioperative Medicine, Groote Schuur Hospital, University of Cape Town, South Africa*

Corresponding author, email: j.lazarus@uct.ac.za

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Introduction

A 2014 editorial in European Urology posed the question: "Enhanced recovery after surgery: are we ready, and can we afford not to implement these pathways for patients undergoing radical cystectomy?"[1] Until recently, our uro-oncology unit would have had to answer clearly that we were not ready. However, perhaps more tellingly, until recently we were unaware of the cost to our patients of not implementing enhanced recovery after surgery (ERAS).

Our unit is not alone in our sluggish adoption of ERAS,[2] yet the reasons for this lack of universal uptake are perplexing. What is preventing greater uptake? Is it a theory or implementation problem? Is it our surgical dogma, our belief that we are already doing ERAS, our fear that it may be too much work or concern that it doesn't work?

Radical cystectomy (RC) arguably represents the most morbid operation that urological surgeons undertake. Despite the introduction of minimal access surgical options and improved peri-operative care, we remain aware, in our unit, that outcomes fall short of where they could be. Internationally, morbidity is quoted as ranging from 30–64% and mortality from 1–8% even in high-volume centres.[1] RC patients are typically elderly, comorbid and in our unit, often locally advanced at the time of presentation.

In this paper, we will attempt to answer the questions: What exactly is ERAS? What is the evidence for ERAS? Lastly, we'll define the three key pre-, intra-, and postoperative elements of ERAS.

What exactly is ERAS?

Enhanced recovery after surgery (ERAS) programmes rely on multidisciplinary, multi-component care pathways. ERAS aims to standardise care of patients undergoing RC and other procedures to reduce morbidity and improve operative outcomes.

ERAS now has a substantial body of supportive literature and it is now possible to assert that evidence-based elements of care promote fast-track recovery and contain costs.[1]

Kehlet, a Danish surgeon, who authored a landmark 1997 paper, is regarded as setting out many of ERAS's founding principles. He sought to understand the pathophysiology of surgical trauma. His paper concluded: *"While no single technique or drug regimen has been shown to eliminate postoperative morbidity and mortality, multimodal interventions may lead to a major reduction in the undesirable sequelae."*[3] ERAS relies, as Kehlet predicted, on teams to optimise the outcomes of a patient undergoing major cancer surgery. He also argued for the importance of "preventive analgesia".

Much of the literature supporting ERAS comes from the colorectal community, but urological surgeons are not far behind.

What is the evidence for ERAS?

The Southampton group documented their initial experience with ERAS for RC. They summarised the impact of ERAS as an *"aggregation of marginal gains"*. They documented a halving of their patient's length of stay (LOS). Multiple small changes, it could be concluded, led to a big impact on this important outcome measure.[4]

Another good example of what can be achieved with the implementation of ERAS to RC came from Maffezzini et al.[5] They applied six ERAS components (no oral mechanical bowel preparation, epidural analgesia, antimicrobial prophylaxis, standard anaesthetic protocol, preventing intraoperative hypothermia, and early nasogastric tube removal) to 71 patients. When compared with historical controls, patients with ERAS had a reduced time to diet (from seven to four days) and shorter LOS (from 22 to 15 days) without worsening morbidity.[1,2]

A recent comprehensive overview of evidence-based interventions utilised in ERAS programmes can be found in a review by Azhar et al.[2] Figure 1 summarises some of the headline ERAS outcomes.

The first randomised controlled trial (RCT) comparing ERAS-treated RC patients with non-ERAS was published in 2014.[6] It concluded that ERAS was associated with significant improvement in quality of life (QOL) and decreased postoperative morbidity, demand for analgesia, and stay in the ICU.

Lastly, ERAS raises an old debate: Is it the surgeon or the setting? Which impacts outcome more? A metanalysis considered the relationship between hospital/surgeon volume and outcome for RC. It concluded that postoperative mortality after cystectomy is significantly inversely associated with high-volume hospitals.[7]

How to: The ERAS primer

Instituting ERAS involves identifying a multidisciplinary team that includes nursing staff, high care staff, anaesthetists, dieticians, physiotherapists and hospital management. The appointment of a

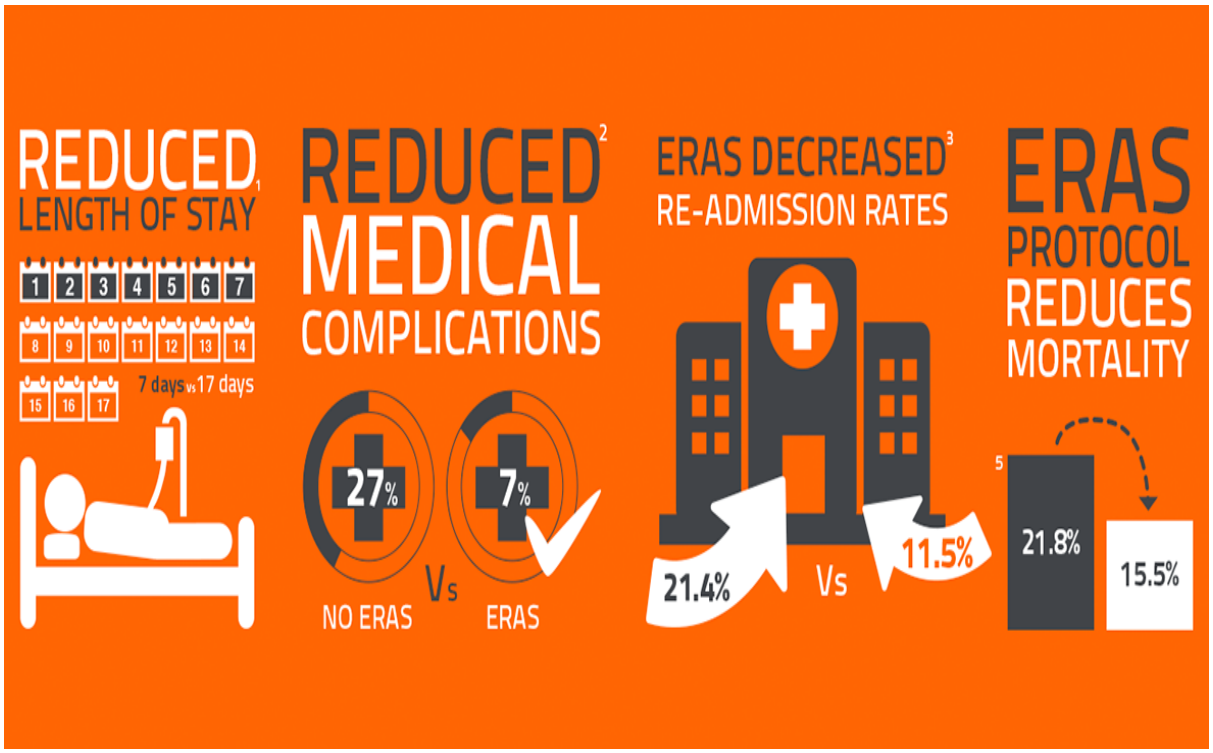

Figure 1: Documented impact of ERAS pathways on outcome metrics[8]

dedicated ERAS sister has proven invaluable in initiating ERAS, but the leadership of the team remains the responsibility of the urological surgeon.

Compelled by the data, our team resolved to follow the international ERAS society protocol. However, we soon realised that certain aspects were not appropriate in our setting. Examples include lack of access to preoperative alvimopan – an opioid receptor antagonist and limited preoperative optimisation. We met regularly as a team and scrutinised each aspect of the ERAS protocol, identified barriers to implementation and tweaked certain aspects to our setting. The outcome of this was the development of our own ERAS protocol.

To assist with compliance of this protocol, we developed a set of posters that summarise the ERAS RC protocol. It is a useful reference that we have put up in our ward, clinics and in theatre as a visual reminder. We feel this has assisted compliance. A copy of these posters is available as a download (Appendix A).

Additionally, useful comprehensive documents outlining ERAS in RC have been drawn up by the British Association of Urological Surgeons (BAUS) and the ERAS society.[9,10] However, meeting regularly as an ERAS team to review local data and monitor implementation brings these protocols into practice.

Below is a primer of the three key components of each of the pre-, intra-, and postoperative ERAS goals:

A) Preoperative

1) Patients should receive **dedicated verbal counselling.** We have produced a document entitled "*Your guide to enhanced recovery*" (Appendix B) which empowers the patient to engage in the ERAS process. Patients should meet a stoma therapist, ERAS-trained nursing sister and a dietitian (often Fresubin shakes are provided for home use).

2) **Vigorous preop optimisation** of comorbid conditions.

- Anaemia is vigorously targeted. Transfusion is a recognised immunosuppressant and an independent risk factor for comorbidities such as sepsis, pulmonary and renal failure, infections and even cancer recurrence and mortality.[11] Causes of anaemia are sought and iron deficiency anaemia is treated with appropriate iron therapy, depending on time to surgery. If there is no response to oral iron, intravenous preparations such as low molecular weight iron dextran (CosmoFer is administered as a total dose infusion [TDI] for rapid delivery). Under 40 kg TDI of 500 mg (10 ml) and above 40 kg TDI of 1 000 mg (20 ml) is used.
- Smoking cessation and alcohol reduction. It is recommended that patients stop smoking a minimum of four weeks prior to surgery. It is not recommended to stop smoking in the week prior to surgery as this increases airway secretions and reactivity.
- Sarcopaenia is associated with an increased risk of cancer death and all-cause mortality at 90 days (8% vs 2%).[12] Thus, nutritional support is most important. Physical exercise is encouraged as part of the prehab process.

3) **On the day before surgery:** Bowel prep should be omitted. Preoperative carbohydrate loading (clear electrolyte/carbohydrate-containing liquids) up to two hours prior to surgery is administered to all non-diabetic patients. It is safe and has been shown to reduce recovery times.[2] Prolonged fasting is avoided and clear fluids up to two hours before anaesthesia should be encouraged. Sedative premedications are avoided. Thromboprophylaxis includes TED stockings, as well as Clexane administration 12–24 hours post-

operatively which should be continued for four weeks.[13] Renal adjustment is only required if CrCl < 30 ml/min.

B) Intraoperative

1) **Anaesthesia:**

- Opioids used for intra- and postoperative analgesia are frequently associated with adverse effects including nausea and constipation. These adverse effects prevent smooth postoperative recovery. We aim to utilise opioid-sparing anaesthesia. Although epidurals have been advocated as part of an ERAS programme, some patients are not amenable to an epidural and some goals of ERAS may not be met by routine epidural use. We favour general anaesthesia in combination with neuraxial long-acting opioids (morphine with or without bupivacaine), wound infusion catheters (postoperative), and parenteral paracetamol and NSAIDs (paracoxib) within the context of a multimodal analgesia regimen. For top-up, patient-controlled analgesia using short-acting opioids (fentanyl) may be prescribed. Intraoperative lignocaine infusions may also be utilised.
- An RCT has shown that restrictive intraoperative fluid regimens were associated with lower transfusion, fluid replacement requirements, and a 35% decrease in complications.[1,14] A zero-balance approach using goal-directed fluid therapy should be utilised, avoiding overhydration and making judicious use of vasopressors.
- The use of tranexamic acid in RC to reduce transfusion rates is presently the subject of the TACT trial. Its use in open radical prostatectomy resulted in a 21% reduction in transfusion.[15]
- Hypothermia and nasogastric (NG) intubation is avoided. A Cochrane metanalysis of 37 trials showed that the use of NG tubes increased vomiting after abdominal surgery.[16] Monitoring core temperature and targeting normothermia via means such as forced air warmers should be mandatory.

2) **Minimal access surgery:** The use of a laparoscopic/robotic approach is supported by a recent metanalysis.[17] The study showed that cancer control outcomes are comparable between robotic and open techniques, supporting the oncological safety. Blood loss was reduced and operative time longer for the robotic approach. Similar rates of postop complications and length of stay were seen. This illustrates that complications are related to the conduit rather than the approach to RC.

In addition to laparoscopy, we have also incorporated an open extraperitoneal approach into our practice which has also been shown to produce improved outcomes.[18]

We have evolved our practice to make selective use of cutaneous ureterostomy diversion. There is a body of literature to support ureterostomy diversion. It was also the subject of a recent favourable British Journal of Urology International (BJUI) editorial.[19] Ureterostomy is also the subject of an ongoing trial comparing its outcomes to ileal conduit.[20]

3) **Surgical team:** Since a review of outcomes at our institution in 2016,[21] we mandate two consultant surgeons to be present for this prolonged operation. While not a component of ERAS, we feel this decision impacts patient safety positively.

C) Postoperative

1) **Preservation of gastrointestinal function:**

- Early enteral feeding (usually with Fresubin shakes). We start four hours postop with one Fresubin shake (300 kCal) and oral feeds on Day 1 plus two Fresubin shakes. A Cochrane systematic review of early feeding showed no increase in complication, no anastomotic leak, earlier return of bowel function and drips down and that vomiting is not a contraindication to feeding.[22]
- Use of chewing gum, coffee, and laxatives.
- Aggressive targeting of postop nausea and vomiting with up to three antiemetic agents. Of note, patients report nausea and vomiting in 30–70%, while doctors only report it in 20–30% of cases. Our stepwise regimen is:
  - Ondansetron 4–8 mg 8 hrly ivi, and if no response:
  - Metoclopramide 10 mg 8 hrly ivi
  - Prochlorperazine 12.5 mg 8 hrly ivi
- Pre-emptive opioid-sparing analgesia.
- Alvimopan is an opioid receptor antagonist. Its use has been associated with a reduced LOS and faster recovery of bowel function after RC. Unfortunately, it is unavailable in South Africa and its use internationally is hampered by cost.

2) **Standardised postop checklist:**

- Early enforced ambulation (> 1 hr out of bed on Day 1 post surgery is ERAS compliant).
- PEEP bottle.
- Transurethral catheters are removed as early as possible. Likewise, abdominal drains and stents (ideally postop Day 5) are removed early.[1]

3) **Audit:** We enrol all our RC patients prospectively in the international database.[23] This is performed by our ERAS-trained nursing sister whose time we share with colorectal surgery. This allows us to track our compliance and outcomes online. We plan to publish our data soon.

Conclusion

ERAS is a tool to focus multidisciplinary efforts on patient outcomes following RC. As a whole, ERAS may be greater than the sum of its parts. Our challenge as urological surgeons is to lead the multidisciplinary team in a change in our processes. This change essentially is to highly protocolised care pathways.

We need, lastly, to also identify barriers to be overcome to achieve these real-world outcome benefits for our patients.

Conflict of interest

The authors declare no conflict of interest.

ORCID

J Lazarus https://orcid.org/0000-0003-2417-8332
J Howlett https://orcid.org/0000-0003-2495-723X

AS Salukazana https://orcid.org/0000-0003-1726-0370
S Bannister https://orcid.org/0000-0001-9218-9098
M Gibbs https://orcid.org/0000-0002-3283-2552

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Annexures available online.