

Module 17.2

Managing Surgical Stress: Principles of Enhanced Recovery and Effect on Outcomes

Olle Ljungqvist, MD, PhD
Professor of Surgery
Faculty of Medicine and Health
School of Health and Medical Sciences
Department of Surgery
Örebro University
Örebro, Sweden

Kenneth C H Fearon, MD, FRCS
Professor of Surgical Oncology
University of Edinburgh
Clinical and Surgical Sciences (Surgery)
51 Little France Crescent
Edinburgh
Scotland EH16 4SA

Learning Objectives

- Understand the key concepts underpinning modern perioperative care;
- Know the principle domains within an ERAS protocol (pain, GI function and mobilisation);
- Be able to discuss practical aspects of patient management to manage surgical stress and attain optimal organ function and recovery in the perioperative period;
- Understand the importance of the multidisciplinary team, unit organisation, patient information, discharge criteria and audit within an ER programme;
- Gain insight into the key **outcomes** that are possible with an ERAS approach.

Contents

1. Introduction
2. ERAS: the core concept
3. The multidisciplinary team
4. Elements of the ERAS protocol with a focus on stress management
5. Unit organisation/patient information
6. Discharge criteria
7. Audit
8. Implementation and compliance
9. Outcomes
10. Summary
11. References

Key Messages

- Enhanced recovery is simply integrated, evidence-based, modern perioperative care;
- All patients undergoing major surgery should receive optimal nutritional and metabolic care to maintain homeostasis and promote rapid recovery.

1. Introduction

The development and improvement of perioperative care in the last 10-15 years has made it possible to completely revise perioperative nutritional care for most patients. With the introduction of Enhanced Recovery After Surgery (ERAS) protocols for most major surgical procedures, both the metabolic and functional circumstances for nutritional care have greatly improved. In this change of care, nutritional and metabolic care is a key component. In order to successfully apply modern perioperative care, it is essential to understand the basis of ERAS and to change practice from traditional care to modern practice according to ERAS protocols. This module gives an overview of the ERAS protocols and how they impact nutritional and metabolic care and outcomes.

Traditional peri-operative care has generally accepted that a stress response to major surgery is inevitable. This concept was challenged with the view that a substantial element of the stress response can be avoided with the appropriate application of modern anaesthetic, analgesic and metabolic support techniques (1). These changes minimize the catabolic response to the surgery and allow nutrients to be handled in a more normal way than in traditional care where severe stress was prevailing. Conventional postoperative care has also emphasised prolonged rest for both the patient and his/her gastrointestinal tract. Similarly, this concept has recently been challenged. This conceptual change has major impact on the patient's nutritional and metabolic care. In the catabolic patient, medium-term functional decline will ensue if active steps are not taken to return the patient to full function as soon as possible. These two concepts have been combined to produce a new view of how surgical patients should be cared for (the Enhanced Recovery After Surgery (ERAS) protocol). Using a multidisciplinary team approach with a focus on stress reduction and promotion of return to function, an ERAS protocol aims to allow patients to recover more quickly from major surgery, avoid medium-term sequelae of conventional postoperative care (e.g. decline in nutritional status and fatigue), reduce the risk of complications, and reduce health care costs by reducing hospital stay.

The move from traditional peri-operative care to an ERAS protocol is not straightforward. None of the elements within ERAS protocols have been proven to be pivotal in randomised trials. However, the Enhanced Recovery After Surgery (ERAS) group produced a comprehensive consensus of approximately 20 elements for patients undergoing colorectal resection in 2005 (2). This protocol has been tested extensively, and a prospectively audited case-series including >2000 colon and rectal resection patients was published in 2015 (3), just recently reinforced by a nationwide study in Spain (4). The protocol for colonic resections has been updated several times, and the latest edition was published in 2018 (5).

To date, the most frequently used model for ERAS has been open colorectal resection. However, there is no doubt that the same principles can be applied successfully to most other forms of major surgery [for an overview of current procedure specific ERAS®Society guidelines: www.erassociety.org]. Equally, the last 20 years has seen the revolution in laparoscopic surgery making a real impact on the rate at which patients recover from procedures such as cholecystectomy or colorectal resection. The key issue is to combine minimal access surgery with enhanced recovery to achieve optimum outcomes.

2. ERAS: the Core Concept

The core concept in enhanced recovery is to maintain homeostasis and organ function throughout the patient's surgical journey. The key question to be asked by all involved is "what is keeping my patient from recovering and going home?" The four domains thought to be critical for recovery are:

- pain control
- gut function
- mobilisation
- and to avoid complications

Every action of all staff involved in the multidisciplinary care of surgical patients must be focused on how to deliver optimal care in these domains. Pain control aims to keep the patient pain free throughout the recovery, initially with the use of thoracic epidurals if open surgery, regional blocks or IV lidocaine, and later on with oral analgesics. Gut function will be supported by avoiding opioids and nausea, and by maintaining neutral fluid balance to allow intake of fluids and normal food and the return of bowel movements as soon as possible. Also, patients should be mobilised as quickly as possible aiming to return to normal preoperative levels as soon as possible.

3. The Multidisciplinary Team

In order to implement an ERAS protocol there must be an enthusiastic multidisciplinary team. Members of the team necessarily include nurses, anaesthetists and surgeons. However, it is vital to include the co-ordinated help from dieticians, physiotherapists and occupational therapists. It is also important to involve members of staff working at every station/unit that the patient will pass during his/her surgical treatment journey. Equally, the success of a programme will certainly depend on the involvement of hospital management. Implementation is often a radical and sometimes painful process and no member of the team should be focussed on one single area of the patient's journey. Every member of the team should be trying to optimise outcome right from the first attendance at the out-patient clinic to the time of discharge home and jointly take responsibility for functionality of the entire process. A useful tool in implementing ERAS is the use of audit of a combination of outcomes and care processes.

4. Elements of the ERAS Protocol

The ERAS protocol starts already before the patient is admitted to the hospital. At the clinic nutritional screening is done, alongside optimising patients for surgery in all aspects known to improve the outcomes. This includes medical optimisation of co-morbidities (which is beyond the scope of this chapter to discuss), but also to support smoke cessation in smokers, and alcohol abstinence in patients with overconsumption of alcohol. These measures have shown to effectively reduce complications when initiated 4 weeks before the operation. A novel development is the prehabilitation programmes that involve relatively light physical training, both anaerobic and aerobic, alongside nutritional management with protein intake and mental preparation. These programmes have been shown to improve physical function especially in older and frail patients (6).

In the preadmission phase, the immediate preoperative, intraoperative and postoperative periods, individual protocol elements combine to optimise perioperative fluid balance, provide dynamic analgesia, enforce early mobilisation and encourage early oral feeding. Evidence for the efficacy of these individual protocol elements is often extrapolated from traditional care pathways (2, 5). It is important to appreciate that individual protocol elements tend to synergise with each other. Thus, optimal gut function is achieved in open surgery not only with use of a thoracic epidural or IV lidocaine but also when good fluid balance is achieved. If the patient receives excess intravenous fluids to counteract epidural-related hypotension, then any benefit on gut function from the epidural will be overwhelmed by fluid overload and gut-oedema/dysfunction. Insights into and understanding of the fluid balance in the perioperative care has been shown to be very poor and yet of great importance for gut function but also for general outcomes after surgery. This part of the programme is a key to postoperative gut function and is given special attention in the section on gut function (see module 17.3). The following section discusses many of the key individual elements of the ERAS approach and tries to put each in context with the others.

Perioperative fluid balance may be optimised through avoiding routine mechanical bowel preparation (7, 8), restricting unnecessary preoperative fasting (9) and providing preoperative oral carbohydrate loading (10). In the postoperative period intravenous fluid and sodium provision is balanced and instead of intravenous delivery of fluids oral fluids are favoured and should be commenced after the operation on the day of surgery or at the latest on the first postoperative day. Hypotension related to epidural anaesthesia can be treated with judicious use of a vasopressor (11). Individually these elements have been shown to reduce preoperative anxiety (12), improve postoperative insulin sensitivity (1) and reduce complications and length of stay (13).

Within an ERAS protocol anaesthesia based on intravenous or short acting volatile agents is favoured along with avoidance of pre-anaesthetic sedating medication (14). These measures help to reduce both the delays to mobilisation and to oral intake in the immediate postoperative period. In open surgery, intraoperative epidural analgesia, achieves both analgesia and sympathetic blockade which will contribute to a reduction in the postoperative stress response, insulin resistance (15) and gut paralysis (16). Epidural analgesia in the postoperative period provides dynamic analgesia for major open surgery (17) without the side-effects of sedation.

The advances in laparoscopic surgery beyond simple cholecystectomy to colorectal resections, liver and even pancreatic surgery have been accompanied by the recognition

that an epidural is no longer needed during most minimal access surgery and may be replaced by techniques such as one shot spinal diamorphine (18) or intravenous lidocaine infusion (19). Various nerve blocks are also being evaluated as alternatives for local or regional pain management. Step-down analgesia is usually oral paracetamol and non-steroidal anti-inflammatory drugs. Careful management of the transition between epidural and oral analgesia is key to minimising the exposure of patients to systemic opioids. This is an important aspect of the entire care protocol and especially for the return of gut function. Opioids have a series of side effects that negatively affect gut function; they cause gut paralysis, nausea and in many cases vomiting. In addition to these immediate effects, in some countries where over-prescription has been common, the perioperative use of opioids has led to long term opioid addiction.

Early postoperative feeding is encouraged (20) in the presence of a multi-modal anti-ileus package (16), even in the presence of an intestinal anastomosis. It has long been known that early oral/enteral feeding has been associated with a reduced postoperative stay (21). Postoperative oral nutritional supplements are provided as they are of clear benefit in malnourished patients (22) and may benefit patients who are not malnourished (23, 24). When used in combination with preoperative carbohydrate loading and epidural analgesia enteral feeding has been shown to allow the maintenance of nitrogen equilibrium even after major colorectal surgery (25). Elements of the ERAS protocol aim specifically to reduce postoperative nausea, vomiting and ileus. Routine intraoperative and postoperative antiemetics and reduced exposure to systemic opiates are important (26, 27). Avoiding opioids has also the advantage of avoiding the risk of over-use and addiction, a problem recognized as a major health problem in the USA recently. This is combined with maintenance of fluid balance (28), epidural analgesia (17, 28, 29) or alternative analgesic techniques and early mobilisation. It is the combination of all of the above measures that act in synergy to secure that normal food can form the basis for the nutritional care in the ERAS protocol.

Adjuncts to minimal access surgery include the use of deep neuromuscular blockade (DNB) with agents such as rocuronium allowing reduction in inflation pressures (less haemodynamic upset) and better surgical access. Sugammadex allows almost immediate reversal of DNB at the end of surgery and thus the use of DNB does not prolong anaesthetic time (30). Maintaining optimal tissue perfusion during surgery with goal-directed fluid therapy remains a controversial area in terms of optimising outcomes within an ERAS protocol (31). Avoiding hypothermia remains a mainstay of stress reduction (32).

Peritoneal drains are avoided as they inhibit mobilisation and their use does not reduce the incidence or severity of anastomotic leaks (33). Similarly urinary catheters are removed early; this may be possible within 24 hours of surgery (5). As protracted bed rest increases insulin resistance and muscle loss (along with other medical complications), mobilisation is encouraged and facilitated. Measures generally accepted within traditional care such as antibiotic prophylaxis, thromboprophylaxis, avoidance of routine nasogastric tubes and avoidance of perioperative hypothermia are employed within the ERAS protocol.

Following an ERAS protocol allows gastrointestinal function to recover earlier, nutritional status to be maintained and postoperative exercise tolerance to improve.

5. Unit Organisation / Patient Information

For an ERAS protocol to work well it is important that the surgical unit is re-organised. For example, schedules for theatre should take account of the fact that the ERAS patients should ideally be first on the list so that they have the afternoon and evening to start recovery. Equally, the ward space should be organised so that there is room for the patients to mobilise, and this includes also patients undergoing open surgery who are expected to mobilise with their epidurals (ambulatory epidurals). Moreover, patients should be encouraged to walk to a communal eating area for meals. Food and snacks should be freely available for when patients want to eat.

Explicit preoperative patient information can facilitate postoperative recovery and pain control, particularly in patients who exhibit the most denial and highest levels of anxiety (34). A clear explanation of what is to happen during hospitalisation facilitates adherence to the care pathway and allows timely recovery and early discharge (35, 36). It is recommended that patients are informed both orally and in writing or with videos, and that a relative, friend or care giver is also present when the information is given. Importantly, at this first encounter the patient should also be given a clear role with specific tasks to perform, including targets for food intake and oral nutritional supplements and targets for mobilisation, during the postoperative period (37, 38). Providing a diary for patients to record completion of the targets for each day can help focus both the patient and the staff on the protocol.

6. Discharge Criteria

Patients can be discharged when they meet the following criteria:

- good pain control with oral analgesia
- taking solid food, bowel movements re-established and no intravenous fluids
- independently mobile or at same level as prior to admission
- all of the above, no complication in need of hospital care and willing to go home

The discharge process starts at the preadmission counselling session when it is determined if the patient lives alone and has any special needs (e.g. transport, social support etc). Problems that will delay discharge must be addressed at this time rather than once the patient has been admitted. It is clear that in most centres there is a delay between the time when the patient is recovered functionally and when they are actually discharged home (39). Minimising this delay requires optimal discharge planning and to set expectations for patients and their relatives.

7. Audit

All good surgical practice is based on ongoing audit. It is essential that outcomes are documented, particularly during the introduction of an ERAS programme, but also for the maintenance of a functional ERAS programme. While most high quality registries, as used in several countries, focus on outcomes, audit in ERAS has also included the processes of care in the audit. The processes audited are based on the most current guidelines and help units to identify what they may be missing, but also help them understand why they may have certain outcomes. It is felt that this combination of audit

of both process and outcomes is a key to success when establishing ERAS. This type of audit not only ensures that morbidity and mortality are optimal but that feedback is provided on aspects of the programme that may need further development of infrastructure / staff education.

8. Implementation and Compliance

The determinants of outcome within an ERAS programme are important to know so that protocols can be used to maximum efficiency in the correct groups of patients. It is evident that a protocol is not enough to implement an ERAS programme and that compliance with the protocol both pre-op and post-op is vital if good results are to be obtained (39). Compliance is a complex issue that requires audit of the process throughout the patient's journey, ongoing motivation from the team leaders, support from the hospital managers and regular/ongoing (re-)education of staff. Equally, it is evident that although good functional recovery may be obtained with experience and protocol compliance, the organisation of healthcare services to facilitate discharge into the community needs to be optimal if the delay between a patient's functional recovery and their actual discharge date is to be kept to a minimum.

9. Outcomes

Enhanced recovery after surgery (ERAS) protocols have been developed to address the sequelae of the metabolic response to elective surgery and to accelerate recovery by attenuating the stress response and maintain homeostasis so that the length of hospital stay and the incidence of postoperative complications and mortality can be reduced, with the added benefits of reducing healthcare costs. These outcomes are difficult to address in small individual trials from single centres. Meta-analysis has, however, reported on sixteen randomised trials of patients (n=2,376) undergoing major elective open colorectal surgery (40). The length of hospital stay was reduced by 2.3 days and non-surgical complication rates were significantly reduced by 60%. There were no statistically significant differences in readmission or mortality rates. Such evidence suggested already several years ago that ERAS pathways do indeed reduce the length of stay and complication rates after major open colorectal surgery without compromising patient safety. Several follow-up meta-analyses show basically the same results for colorectal surgery, and other meta-analyses from non-colorectal surgery confirm the benefits for recovery in many other types of surgery (41).

What is of particular interest is the marked improvement in nutritional care that is reported with the implementation of ERAS (42). With ERAS significant improvements were found in nutritional screening preoperatively resulting in more patients receiving perioperative nutrition both pre- and postoperatively. The rate of pre-operative carbohydrate treatment instead of fasting was much improved, and, in combination, these changes were associated with better overall outcomes.

Evidence from the literature has repeatedly reported that an ERAS pathway seems to reduce the overall healthcare cost (43, 44). From a health economics point of view, the data suggest that, with the decrease in complications and hospital stay and similar readmission rates, the cost of treatment per patient would be significantly lower for those

treated within an ERAS pathway than those receiving traditional care, despite the need for dedicated staff to implement the pathway.

ERAS programmes have developed considerably since they were first initiated by Kehlet in the 1990s. The individual elements that make up such programmes will continue to evolve. However, it would now appear that current programmes can indeed minimise the adverse impacts of surgery and its sequelae and that limiting factors that may dominate in the future will be related to pre-existing comorbidity and old age. Nonetheless, evidence has emerged to suggest that ERAS protocols may reduce the risks of some comorbidities and risk factors (45) especially when combined with minimal invasive surgery (46). Such issues constitute some of the real challenges for ERAS protocols in the future.

10. Summary

Optimal nutritional and metabolic care (with a focus on stress reduction) should be provided for all patients undergoing major surgery. In a modern context this is best provided within a multimodal care pathway that aims to maintain homeostasis and optimise recovery of organ function. In addition to an evidence-based protocol, such an enhanced recovery pathway requires unit re-organisation, education of staff, repeated implementation, and monitoring of protocol compliance and outcomes.

11. References

1. Ljungqvist, O., Jonathan E. Rhoads lecture 2011: *Insulin resistance and enhanced recovery after surgery*. JPEN J Parenter Enteral Nutr, 2012. 36(4): p. 389-98.
2. Fearon, K.C., et al., *Enhanced recovery after surgery: A consensus review of clinical care for patients undergoing colonic resection*. Clin Nutr, 2005. 24(3): p. 466-77.
3. *The Impact of Enhanced Recovery Protocol Compliance on Elective Colorectal Cancer Resection: Results From an International Registry*. Ann Surg, 2015. 261(6): p. 1153-9.
4. Ripolles-Melchor, J., et al., *Association Between Use of Enhanced Recovery After Surgery Protocol and Postoperative Complications in Colorectal Surgery: The Postoperative Outcomes Within Enhanced Recovery After Surgery Protocol (POWER) Study*. JAMA Surg, 2019.
5. Gustafsson, U.O., et al., *Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS((R))) Society Recommendations: 2018*. World J Surg, 2019. 43(3): p. 659-695.
6. Carli, F., et al., *Surgical Prehabilitation in Patients with Cancer: State-of-the-Science and Recommendations for Future Research from a Panel of Subject Matter Experts*. Phys Med Rehabil Clin N Am, 2017. 28(1): p. 49-64.
7. Guenaga, K.F., et al., *Mechanical bowel preparation for elective colorectal surgery*. Cochrane.Database.Syst.Rev., 2003(2): p. CD001544.
8. Jung, B., et al., *Preoperative mechanical preparation of the colon: the patient's experience*. BMC surgery, 2007. 7: p. 5.
9. Brady, M., S. Kinn, and P. Stuart, *Preoperative fasting for adults to prevent perioperative complications*. Cochrane database of systematic reviews (Online), 2003(4): p. CD004423.

10. Ljungqvist, O., *Modulating postoperative insulin resistance by preoperative carbohydrate loading*. Best Practice and Research: Clinical Anaesthesiology, 2009. 23: p. 401-409.
11. Holte, K., et al., *Epidural anesthesia, hypotension, and changes in intravascular volume*. Anesthesiology, 2004. 100(2): p. 281-6.
12. Hausel, J., et al., *A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients*. Anesth Analg, 2001. 93(5): p. 1344-50.
13. Awad, S., et al., *A meta-analysis of randomised controlled trials on preoperative oral carbohydrate treatment in elective surgery*. Clinical Nutrition, 2012.
14. Møiniche, S., H. Kehlet, and J.B. Dahl, *A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia*. Anesthesiology, 2002. 96(3): p. 725-41.
15. Uchida, I., et al., *Effect of epidural analgesia on postoperative insulin resistance as evaluated by insulin clamp technique*. The British journal of surgery, 1988. 75(6): p. 557-62.
16. Bragg, D., et al., *Postoperative ileus: Recent developments in pathophysiology and management*. Clin Nutr, 2015. 34(3): p. 367-76.
17. Marret, E., et al., *Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery*. The British journal of surgery, 2007. 94(6): p. 665-73.
18. Levy, B.F., et al., *Randomized clinical trial of epidural, spinal or patient-controlled analgesia for patients undergoing laparoscopic colorectal surgery*. British Journal of Surgery, 2011. 98(8): p. 1068-78.
19. Venthham, N.T., et al., *Efficacy of Intravenous Lidocaine for Postoperative Analgesia Following Laparoscopic Surgery: A Meta-Analysis*. World J Surg, 2015. 39(9): p. 2220-34.
20. Lewis, S.J., et al., *Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials*. BMJ, 2001. 323(7316): p. 773-776.
21. Andersen, H.K., S.J. Lewis, and S. Thomas, *Early enteral nutrition within 24h of colorectal surgery versus later commencement of feeding for postoperative complications*. Cochrane.Database.Syst.Rev., 2006(4): p. CD004080.
22. Beattie, A.H., et al., *A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients*. Gut, 2000. 46(6): p. 813-818.
23. Keele, A.M., et al., *Two phase randomised controlled clinical trial of postoperative oral dietary supplements in surgical patients*. Gut, 1997. 40(3): p. 393-399.
24. Smedley, F., et al., *Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care*. Br J Surg, 2004. 91(8): p. 983-90.
25. Soop, M., et al., *Randomized clinical trial of the effects of immediate enteral nutrition on metabolic responses to major colorectal surgery in an enhanced recovery protocol*. Br J Surg, 2004. 91(9): p. 1138-45.
26. Apfel, C.C., et al., *Comparison of predictive models for postoperative nausea and vomiting*. Br J Anaesth, 2002. 88(2): p. 234-40.
27. Carlisle, J.B. and C.A. Stevenson, *Drugs for preventing postoperative nausea and vomiting*. Cochrane database of systematic reviews (Online), 2006. 3: p. CD004125.

28. Raghunathan, K., M. Singh, and D.N. Lobo, *Fluid management in abdominal surgery: what, when, and when not to administer*. Anesthesiol Clin, 2015. 33(1): p. 51-64.
29. Jørgensen, H., et al., *Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery*. Cochrane database of systematic reviews (Online), 2000(4): p. CD001893.
30. Madsen, M.V., et al., *Neuromuscular blockade for optimising surgical conditions during abdominal and gynaecological surgery: a systematic review*. Acta Anaesthesiol Scand, 2015. 59(1): p. 1-16.
31. Minto, G., M.J. Scott, and T.E. Miller, *Monitoring needs and goal-directed fluid therapy within an enhanced recovery program*. Anesthesiol Clin, 2015. 33(1): p. 35-49.
32. *Hypothermia: prevention and management in adults having surgery*. NICE guidance, clinical guideline, CG 65, 2008.
33. Karliczek, A., et al., *Drainage or nondrainage in elective colorectal anastomosis: a systematic review and meta-analysis*. Colorectal Dis, 2006. 8(4): p. 259-65.
34. Kiecolt-Glaser, J.K., et al., *Psychological influences on surgical recovery. Perspectives from psychoneuroimmunology*. Am Psychol, 1998. 53(11): p. 1209-18.
35. Halaszynski, T.M., R. Juda, and D.G. Silverman, *Optimizing postoperative outcomes with efficient preoperative assessment and management*. Crit Care Med, 2004. 32(4 Suppl): p. S76-86.
36. Forster, A.J., et al., *Effect of a nurse team coordinator on outcomes for hospitalized medicine patients*. Am J Med, 2005. 118(10): p. 1148-53.
37. Disbrow, E.A., H.L. Bennett, and J.T. Owings, *Effect of preoperative suggestion on postoperative gastrointestinal motility*. West J Med, 1993. 158(5): p. 488-92.
38. Blay, N. and J. Donoghue, *The effect of pre-admission education on domiciliary recovery following laparoscopic cholecystectomy*. Aust J Adv Nurs, 2005. 22(4): p. 14-9.
39. Maessen, J., et al., *A protocol is not enough to implement an enhanced recovery programme for colorectal resection*. Br J Surg, 2007. 94(2): p. 224-31.
40. Greco, M., et al., *Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials*. World J Surg, 2014. 38(6): p. 1531-41.
41. Visioni, A., et al., *Enhanced Recovery After Surgery for Noncolorectal Surgery?: A Systematic Review and Meta-analysis of Major Abdominal Surgery*. Ann Surg, 2018. 267(1): p. 57-65.
42. Martin, L., et al., *Implementation of an Enhanced Recovery After Surgery Program Can Change Nutrition Care Practice: A Multicenter Experience in Elective Colorectal Surgery*. JPEN J Parenter Enteral Nutr, 2019. 43(2): p. 206-219.
43. Kariv, Y., et al., *Clinical outcomes and cost analysis of a "fast track" postoperative care pathway for ileal pouch-anal anastomosis: a case control study*. Dis Colon Rectum, 2007. 50(2): p. 137-46.
44. Ljungqvist, O., N.X. Thanh, and G. Nelson, *ERAS-Value based surgery*. J Surg Oncol, 2017. 116(5): p. 608-612.
45. Jorgensen, C.C., S. Madsbad, and H. Kehlet, *Postoperative morbidity and mortality in type-2 diabetics after fast-track primary total hip and knee arthroplasty*. Anesth Analg, 2015. 120(1): p. 230-8.
46. Pedziwiatr, M., et al., *Is ERAS in laparoscopic surgery for colorectal cancer changing risk factors for delayed recovery?* Med Oncol, 2016. 33(3): p. 25.