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Enhanced Recovery After Surgery: Hepatobiliary

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INTRODUCTION

Enhanced Recovery After Surgery (ERAS) is a multidisciplinary, evidence-based approach to perioperative management. Originally implemented in colorectal surgery, the movement to optimize the care of surgical patients has expanded to most surgical subspecialties, including hepatopancreatobiliary (HPB) surgery.^{1–4} Central to the concept of ERAS is reduction of the typical physiological neuroendocrine stress response to surgery (Figure 1).^{5,6} By targeting specific aspects of the preoperative, intraoperative, and postoperative care, ERAS protocols create a cohesive pathway that effectively returns patients to normal homeostasis. The major goal of the ERAS initiative is to rapidly and safely return a patient to his or her baseline function after the stress of a surgical operation.

Key to enhancing patient recovery is multi-disciplinary involvement and participation of all care-team members, including the patient and caregiver(s). The importance of patient engagement and education cannot be over-emphasized, as it serves as the foundation for the entire ERAS initiative. Only with the support of the patient, can the “pillars” of enhanced recovery stand. These pillars, essentially part of every ERAS pathway, are early postoperative feeding, goal-directed fluid therapy, non-narcotic analgesia, and early ambulation (Figure 2). Of course, fundamental surgical concepts applicable to all operations continue to have relevance, including preoperative thromboembolic prophylaxis, appropriate antibiotic dosing, and the location and size of the surgical incision.

Historically, the ERAS literature has focused on outcomes such as length of stay (LOS) and complications.⁷ However, the focus has begun to shift toward patient-reported outcome

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measures and long-term results such as return to intended oncologic therapy after oncologic resection. Additionally, measures such as cost effectiveness and compliance are emerging. Finally, it is important to recognize that ERAS is a dynamic system of care that responds and evolves as new evidence emerges.

CORE COMPONENTS OF ERAS

The Foundation: Patient Evaluation, Education, and Engagement

As with any preoperative evaluation, the first steps in evaluating a patient for an enhanced recovery protocol are a preoperative history and physical exam. Providers should perform a detailed review of comorbidities that may result in an increased risk of adverse outcomes after general anesthesia and hepatobiliary surgery, including advanced age, pre-existing lung or heart disease, and/or signs of portal hypertension. The presence of these and other medical conditions contributing to “borderline operability” should be, when possible, optimized in attempt to prevent complications.^{8,9} Particular attention should be given to preoperative medications, including the use of anticoagulants, steroids, and narcotics, as their use may contribute to poor outcomes and challenges to ERAS implementation.^{10,11} For cancer patients, a thorough review of oncologic history including prior radiation, previous resections, intra-arterial therapies, and the administration of chemotherapy (both preoperative or planned future treatment) should be described.

To determine each patients’ functional status, at minimum, a validated tool such as the Eastern Cooperative Oncology Group (ECOG) Performance Status should be used.^{12,13} With the aging population and increases in the use of potentially debilitating preoperative systemic therapy, measurement of preoperative frailty is strongly recommended.^{14,15} While the factors that define ‘frailty’ have not been precisely defined, clinicopathologic factors such as age, preoperative albumin level, and sarcopenia have been associated with postoperative morbidity.^{16–18} Objective and validated measures of functional capacity such as the Timed Up and Go Test, the 6-minute walk test, and measurement of hand grip strength can prove useful for frailty measurement.^{19–21} In addition, tools such as the Mini Cog or Mini Mental Status Examination may be utilized to screen for neurocognitive dysfunction,^{22–24} and patient-reported outcome tools are useful to determine baseline symptom burden and symptom interference.²⁵ Diagnosing frailty or identifying patients “at risk” via preoperative assessment does not preclude surgical intervention or participation in an ERAS pathway, but it does allow for targeted prehabilitation efforts, prediction of postoperative morbidity, and may guide modifications to multiple aspects of perioperative care.

Paramount to the concept of Enhanced Recovery is patient education and engagement. At the preoperative visit, the patient and his or her caregiver(s) should be educated not only on the operation but on the components of the ERAS protocol. Discussing the basic principles of ERAS and setting expectations substantially facilitate its successful implementation. In particular, the expectations of multi-modal analgesia use, early ambulation and feeding, and timely discharge should be set. Giving each patient the team’s discharge criteria is particularly effective to align patient and provider goals (Box 1). Hard copies of educational materials should be provided to the patient for later reference in education-level appropriate

language to ensure patient understanding. As always, the patient and caregiver should be given many opportunities to ask questions regarding the operation and ERAS protocol prior to providing consent.

Perioperative Nutrition

The assessment of baseline nutritional status is an important component of the preoperative evaluation. A thorough work-up should include questions pertaining to dietary changes and recent weight loss, body mass index (BMI), and the determination of albumin, prealbumin, and/or ferritin levels. According to the ERAS Society guidelines for liver surgery, weight loss > 10-15% within 6 months, BMI < 18.5 kg/m², and serum albumin < 3 g/dL are criteria that merit delay in surgical resection for optimization with supplemental nutrition.²⁶ For patients undergoing oncologic resection, the receipt of neoadjuvant chemotherapy increases the risk of malnutrition and sarcopenia. Whenever possible, both sarcopenia and sarcopenic obesity should be identified and addressed in the preoperative setting to better understand and potentially intervene upon the increased risk of morbidity and mortality.^{14,27}

Despite accepted guidelines regarding preoperative fasting, many patients have been instructed to endure long periods of fasting prior to procedures requiring general anesthesia.²⁸ For elective procedures in patients with normal gastric function, the current American Anesthesiologist's Association (ASA) guidelines recommend clear liquid fasting up to 2 hours and "light" solids up to 6 hours prior to operations requiring general anesthesia.²⁹ This is in accordance with the ERAS Society guidelines specific to liver and pancreas surgery.^{26,30} There is strong evidence to support carbohydrate loading in colorectal surgery to maximize glycogen storage and minimize insulin resistance in the postoperative period.³¹ The data supporting carbohydrate loading prior to hepatobiliary surgery is lacking, however, it is likely beneficial and should be considered particularly prior to pancreaticoduodenectomy.^{26,30} Oral bowel preparation, which can lead to fluid shifts and electrolyte imbalance in the perioperative period, has little evidence or rationale in HPB surgery, and is not recommended.^{26,30,32}

The final key nutritional aspect of ERAS is the initiation of early postoperative feeding. The literature supports early feeding and rapid diet advancement after gastrointestinal surgery and hepatobiliary surgery, in particular.^{26,33–36} Patients without contraindications to oral feeding should be given clear liquids on the day of surgery with plans for advancement to a solid diet on the day following the operation. Prophylactic use of nasogastric tubes should be avoided as this can potentiate aspiration, delay diet advancement, and contribute to unnecessary delays in ambulation and subsequent discharge.^{26,30} If enteric drainage is needed, early removal is recommended. Intravenous fluids should be used judiciously. Measurement of brain natriuretic peptide (BNP) levels has recently been shown to be an accurate measure of euvolemia, and a more accurate guide for postoperative fluid administration.³⁷ Patients tolerating clear liquids ad lib rarely require supplemental fluid administration. Anti-emetic prophylaxis should be administered at the discretion of the anesthesiology team to limit postoperative nausea/vomiting and promote early feeding. The use of perioperative steroids may also be considered to ameliorate the body's stress response to surgery with added antiemetic and analgesic benefits.^{38,39}

Goal-Directed Fluid Therapy

The concept of intraoperative goal-directed fluid therapy (GDFT) utilizes hemodynamic parameters, such as stroke volume variation (SVV) and/or pulse pressure variation, to guide fluid administration. This allows dynamic assessment of intravascular volume status in order to administer the appropriate amount and type of intravenous fluid at the appropriate time and to measure the hemodynamic response to bolus. While the more conventional parameters such as urine output, mean arterial pressure, and central venous pressure (CVP) are important hemodynamic factors, SVV is more accurate in predicting fluid responsiveness intraoperatively. Benefits of GDFT have been demonstrated in a recent randomized clinical trial (RCT) comparing traditional fluid administration to GDFT, where patients treated with GDFT had a lower incidence of postoperative complications.⁴⁰

GDFT principles should carry into the immediate postoperative period, transitioning to the use of trends in urine output and hemodynamic indices to guide resuscitation. In addition, BNP measurement is an important metric that can assist in accurate assessment of intravascular volume status postoperatively. BNP is a 32-amino acid protein produced by the cardiac myocytes in response to dilation in the setting of volume overload. It has been shown to assess intravascular volume status better than changes in BUN/creatinine ratio immediately after pancreatectomy.⁴¹ More recently, a postoperative BNP-guided protocol developed at MD Anderson Cancer Center that includes daily postoperative measurement of BNP levels has been shown to reduce both cardiopulmonary and renal complications after liver surgery (Table 1).³⁷

Non-Narcotic and Neuraxial Analgesia

Multimodal, non-narcotic analgesia is a core component of enhanced recovery. Opioids are not only addictive substances causing a major public-health crisis across the nation, but can also have negative effects on patient experience, function, recovery, and survival. Systemic opioids provide pain relief at the expense of side effects such as drowsiness, nausea, vomiting, xerostomia, gut dysmotility, and respiratory depression. These negative side effects can lead to postoperative morbidity and prolonged hospital LOS.⁴² In cancer patients, research suggests that opioids may play a role in augmenting cancer biology by activating vascular endothelial growth factor (VEGF) via the mu receptor, directly stimulating cancer growth and metastasis.^{43–45} Data from several studies suggest improved oncologic outcomes in patients receiving opioid-sparing analgesic regimens.^{46–49}

ERAS protocols are most effective when they utilize a multimodal opioid-sparing analgesia strategy. Preventative regimens are often used and can consist of preoperative administration of non-narcotic neuromodulators (such as pregabalin), in combination with anti-inflammatory nonsteroidal drugs (NSAIDs, COX-2 inhibitors) and non-addicting opiate-like substances (such as tramadol). There is also strong support for the use of regional analgesia via neuraxial or field blocks covering the incisional area. Epidural placement and other regional blocks should be performed by an experienced practitioner to cover the desired area of incision. Decision-making around these strategies requires continual communication between surgical and anesthesiology teams. The goal of preemptive strategies is to blunt the acute pain of surgical injury, typically lasting ~48 hours so that bolus narcotic dosing can be

avoided. A RCT of 140 patients undergoing hepatobiliary surgery at MD Anderson Cancer Center directly compared thoracic epidural analgesia (TEA) to patient-controlled IV analgesia (PCA), and TEA resulted in markedly less narcotic use, lower pain scores, and superior patient-reported outcomes.⁵⁰ Additional studies have also demonstrated the oncologic benefits of these strategies.^{47,49}

Some concerns surround TEA use in regards to analgesia-related complications, such as hypotension and hypoperfusion. Importantly, the aforementioned trial demonstrated comparable perioperative morbidity without an increase in analgesia-related complications in the TEA group compared to PCA group.⁵⁰ Previous data has also shown TEA leads to decreased incidence of postoperative ileus, decreased risk of postoperative pneumonia, and decreased insulin resistance.^{51–53} An alternative and commonly practiced technique for regional analgesia is a transversus abdominis plane block (TAP block), where local anesthetic is injected under ultrasound guidance within the space between the internal oblique and transversus abdominis. Compared to placebo, TAP block leads to a decrease in narcotic use, lower pain scores, and a decrease in postoperative nausea and vomiting, while avoiding the need for an external delivery catheter.^{54,55} The question of superiority of TEA vs. TAP block for open HPB surgery remains unanswered, with current comparisons of the two modalities in various types of abdominal surgery showing mixed results.^{56,57}

Early Ambulation and Early Removal of Tubes/Drains

Postoperative mobilization, another key aspect of ERAS, should be initiated early after surgery. Though it is a simple intervention, early ambulation can have profound effects on reducing ileus, improving pulmonary function, and decreasing postoperative thromboembolic events.^{26,30} For patients with baseline functional deficits, physical and occupational therapists should be involved early in the postoperative period. Limited placement and early removal of any unnecessary drains, tubes, or catheters are helpful in facilitating this aspect of ERAS. Urinary catheters can be essential in the immediate postoperative period for hemodynamic monitoring and GDFT, but should be removed as soon as patients are ambulatory (typically postoperative day 1-2). For older males, prophylactic alpha blockade can be utilized to avoid urinary retention and subsequent catheter replacement.

Minimally Invasive Approaches to Hepatobiliary Surgery

Experience from specialized, high-volume centers indicates that minimally invasive hepatobiliary surgery is safe and effective.^{58–61} Laparoscopic liver resection (LLR) approaches have been readily adopted and are becoming standard practice for minor liver resections, particularly in the case of left lateral sectionectomies.⁶² In 2009, a large multi-center study demonstrated both feasibility and safety of major laparoscopic liver resections.⁵⁹ This allowed for direct comparison of LLR procedures to those performed via open surgical approach, which highlighted important benefits of small incisions: less pain, decreased postoperative ileus, and lower hernia rates. Importantly, oncologic resection was not compromised by a laparoscopic approach.^{63–66} While there is evidence that ERAS pathways can hasten recovery after laparoscopic surgery compared to non-ERAS care, little evidence exists in regards to superiority of laparoscopy over laparotomy within ERAS

protocols.^{67,68} A recent double-blinded, multicenter RCT comparing laparoscopic vs. open left lateral sectionectomy within an ERAS protocol failed to show any difference between groups in regards to recovery and was terminated early.⁶⁹ For pancreatic surgery, the most commonly performed minimally invasive operation is laparoscopic distal pancreatectomy. Laparoscopic enucleation and laparoscopic pancreaticoduodenectomy are being increasingly reported, as are laparoscopic approaches to the management of pancreatitis.⁷⁰ Research in both laparoscopic distal pancreatectomy and pancreaticoduodenectomy show favorable outcomes.^{71,72} However, selection bias is inherent in these non-randomized analyses. Laparoscopic pancreatic surgery is feasible in particular clinical scenarios, but is largely dependent on operator skill and experience.

For every case being considered for a minimally invasive approach, the safety, efficacy, and efficiency of the procedure must be taken into account. In addition, costs associated with minimally invasive techniques should be considered, as longer operative times and disposable instruments can lead to more charges in laparoscopy than in open surgery, however this may be counteracted by improvements in LOS.⁶⁰ Although the magnitude of impact of ERAS may be less in minimally invasive HPB surgery, the synergy between the perioperative care and the intraoperative approach can be substantial.

OUTCOMES IN HPB AND COMPLIANCE MONITORING

Studies directly comparing enhanced recovery after HPB surgery to traditional care pathways show improvements in various metrics, namely length of stay, pain-related measures, and morbidity. In a randomized trial, Jones et al. demonstrated that ERAS resulted in more timely discharge readiness and shortened LOS compared to standard care after open liver surgery (LOS 4 vs. 7 days; $P < 0.001$). Surgical complications and patient satisfaction were, however, comparable between groups.¹ In a meta-analysis of RCTs comparing ERAS to traditional pathways for liver surgery, complications and LOS were substantially lower for patients treated by enhanced recovery.² A systematic review of ERAS for pancreatic surgery showed that ERAS decreased LOS and readmission rates in the majority of studies compared to standard care. Morbidity was not found to be significantly decreased with ERAS in five of six studies, with the exception of a decrease in DGE with ERAS use after pancreaticoduodenectomy.^{73,74} While these results are promising, it is important to note the variation in how outcomes such as complications were measured and the fact that ERAS criteria were not uniform across the studies.

This issue highlights the important point of compliance monitoring and auditing. ERAS Society guidelines now exist for both liver resection and pancreaticoduodenectomy, creating reference lists of ERAS components stratified by grade of recommendation.^{26,30} While these guidelines are evidence-based, there is little understanding of the impact that each component has on the improvement in outcomes.⁶ Similarly, without uniformity in the definition of ERAS compliance across a specialty, studies cannot be directly compared. The ERAS Compliance Group has shown that higher compliance with ERAS protocols is associated with more substantial benefits in colorectal surgery. Thus, programs should strive not only to implement all recommended components, but also to have a strategy that monitors and reports compliance.^{75,76} Protocol-driven pathways are strongly recommended

as a means of ensuring compliance. An example of an ERAS pathway for liver surgery in large tertiary cancer center is demonstrated in Figure 3. The ERAS Society has developed an auditing system, based on the guidelines, for continuous monitoring of compliance and outcomes.⁵

PATIENT-REPORTED OUTCOMES AND RETURN TO INTENDED ONCOLOGIC TREATMENT (RIOT)

As mentioned, the main goal of any ERAS pathway is to return the patient to his or her baseline function safely and quickly. However, functional recovery is rarely found in the medical record. Only the patient can relate their experience and their functional recovery, and validated patient-reported outcomes (PROs) are the only conduit to record these outcomes. While clinical outcomes research has shown objective improvements with ERAS compared to traditional pathways in regards to LOS, morbidity, and costs, the implementation of PROs allows for an understanding of the effect of ERAS on patient functional and emotional recovery. Validated PRO tools are now a recommended component of ERAS as they provide meaningful data to ensure that changes in practice are improving patient-centric outcomes.^{77,78}

A corollary outcome that holistically captures true functional recovery in surgical oncology patients is return to intended oncologic therapy (RIOT).⁷⁹ This quality metric represents the number of patients who initiate postoperative adjuvant treatment of any kind divided by the number of patients intended to receive adjuvant therapy.^{6,79} Successful tumor resection is a critical piece of oncologic care, but with high rates of multi-disciplinary management of cancer, adjuvant therapies are often recommended.^{79,80} RIOT is an important outcome that can be used to validate the degree of successful recovery. Once a patient has been cleared to resume further oncologic therapy, he or she has crossed a recovery threshold that can have true survival impact. At MD Anderson Cancer Center, the implementation of an ERAS protocol after liver surgery resulted in increased RIOT rates to 95% at 21 days (compared to 87% at 32 days for standard care).⁸¹

SUMMARY

ERAS protocols in hepatobiliary surgery are proven to improve outcomes such as LOS and postoperative complications. Recently, a shift toward analysis of long-term oncologic and patient-centered functional outcomes suggests the superiority in ERAS in these domains compared to traditional recovery, as well. Implementation strategies, compliance measurement and outcomes feedback have the potential to further the efficacy of ERAS in HPB Surgery.

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SYNOPSIS

Enhanced Recovery After Surgery (ERAS) pathways target specific areas within perioperative patient care in a multi-disciplinary and evidence-based manner. Since its inception and the subsequent positive outcomes associated with its use, ERAS has expanded to most surgical subspecialties, including hepatopancreatobiliary surgery. While certain concepts are universal to all ERAS protocols, there are unique areas of emphasis pertaining to the hepatopancreatobiliary specialties, which will be highlighted throughout this article. In addition, some of the less frequently discussed aspects of enhanced recovery, including patient-reported outcomes, recovery assessment, cost, and auditing will be addressed. Central to ERAS in all specialties is its evidence-based foundation; therefore, pathways must continue to evolve and adapt to new discoveries in the field of perioperative care.

KEY POINTS

- The goal of an effective ERAS program is the rapid return of the patient to normal life function, and in the case of patients with cancer, return to intended oncologic therapies (RIOT). Strategies for achieving these goals are minimization of perioperative stress, as well as the need for excessive fluids and narcotics.
- The foundation of ERAS lies in engagement and education of the patient and caregiver. Core components universal to all ERAS include: early oral feeding, goal-directed fluid therapy, non-narcotic analgesia, and early ambulation.
- Outcome reporting of both objective and more subjective, patient-centered, measures is imperative to advance the field, as are compliance monitoring and auditing processes.

Box 1.**Discharge Criteria Form****Medical Criteria**

Independent ambulation
Adequate pain control on oral pain medicine
Tolerance of oral diet
Appropriate return of bowel function
No signs or symptoms of infection
Comorbidities well-controlled

Safety/Satisfaction Criteria

Psychologically ready for discharge
Safe environment/transportation
Demonstrate comfort with home venous thromboembolic prophylaxis administration
Verbalize discharge instructions
Verbalize whom to contact for concerns
Confirm follow-up visit

Figure 1:

The success of ERAS depends on a number of strategies aimed at one vision with a continuous measurement of outcomes. From Manso M, Schmelz J, Aloia T. ERAS-Anticipated outcomes and realistic goals. *J Surg Oncol.* 2017;116(5):570-577; with permission.

Figure 2:

The foundation and pillars of Enhanced Recovery After Surgery. From Kim BJ, Aloia TA. What is “enhanced recovery,” and how can I do it? *Journal of Gastrointestinal Surgery*. 2017;22(1):164-171; with permission.

Factors		Enhanced Recovery Measures
Preoperative	Education	Procedure and ERAS-specific patient education material provided to patient and caregiver.
	Fluid Management	Saline-lock IV in preoperative holding.
	Preoperative Fasting	Clear liquids permitted up to 2 hours prior to surgery. Solids permitted up to 6 hours prior to surgery.
	Bowel State	No mechanical bowel preparation required.
	Preventative Analgesia	Celecoxib 400mg PO, pregabalin 75mg PO (unless age >65 years), tramadol extended release 300mg PO prior to surgery. Anxiolytics and anti-emetic medication as needed per anesthesia team.
Intraoperative	Perioperative Steroids	Dexamethasone 10mg IV administration on induction of anesthesia.
	Opioid Sparing Analgesia	Acetaminophen 1000mg every 6 hours and minimization of narcotic use intraoperatively.
	Total Intravenous Analgesia	IV propofol as main anesthetic agent in conjunction with IV dexmedetomidine, IV ketamine, IV lidocaine, titrated by anesthesiologist as needed.
	Fluid Management	Goal-directed fluid therapy with stroke volume monitoring.
	Regional Anesthesia	MIS: local anesthetic wound infiltration with long-acting bupivacaine. Open: epidural preferred.
	Drains	Limit use to scenarios where absolutely indicated.
Postoperative	Opioid-Sparing Analgesia	Pregabalin, acetaminophen, celecoxib, and tramadol use per protocol in the postoperative period. Hydromorphone 0.5mg IV every 30 minutes PRN breakthrough pain not relieved within 30 minutes of oxycodone administration. PCA only if failure of epidural.
	PRN Analgesia	Epidural titration per pain service. Non-epidural patient: mild pain, acetaminophen 500mg PO every 6 hours; moderate pain, tramadol 50mg PO every 6 hours; severe pain, hydromorphone 0.5mg every 15 min x2
	Tubes & Drains	Limit use of nasogastric tubes. Early removal of foley catheter.
	Early Ambulation	Day of surgery: sit on the edge of bed; POD1 on: out of bed to chair and ambulation at least 4x daily.
	Fluid Management	Hepatobiliary fluid protocol using BUN and UOP monitoring. Minimize IV fluid rate and saline lock after 600cc PO.
	Early Oral Intake	Patients allows clear liquids on day of surgery. Regular diet after POD1.
"Ready for Discharge" Criteria		Formalized discharge criteria: independently ambulatory, pain adequately controlled (on PO medications), oral diet tolerance, appropriate return of bowel function, no signs of infection, well-controlled comorbidities.

Figure 3:

The University of Texas MD Anderson Cancer Center Approach to Enhanced Recovery in Hepatobiliary Surgery; ERAS, enhanced recovery after surgery; IV, intravenous; PO, per os; MIS, minimally invasive surgery; PRN, pro re nata; PCA, patient-controlled IV analgesia; POD, postoperative day; BUN, brain natriuretic peptide; UOP, urine output

Table 1.

BNP-guided resuscitation algorithm for liver surgery

BNP level	Fluid Administration	Other Intervention Indicated
< 100 pg/mL *	250-500 mL bolus Continue current MIVF rate	No
100-200 pg/mL	No bolus Minimize MIVF rate	No
> 200 pg/mL	Minimize MIVF rate or KVO	Consider diuresis and/or cardiac work-up

BNP, brain natriuretic peptide; MIVF, maintenance intravenous fluid; KVO, keep vein open

*
or urine output < 50mL over 2 hours