

# Enhanced Recovery in Gastrointestinal Surgery: Upper Gastrointestinal Surgery

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## Key Words

Enhanced recovery after surgery · Fast-track surgery · Clinical pathways · Liver surgery · Pancreatectomy · Esophagectomy · Gastrectomy

## Abstract

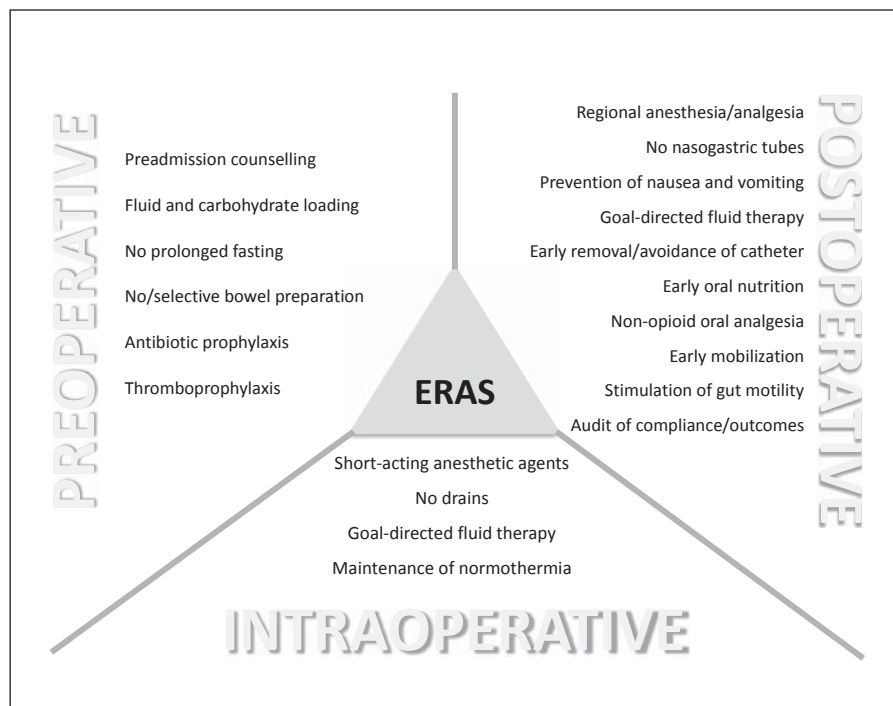
Over the last 20 years, a new concept of perioperative patient care based on a construct of evidence-based interventions referred to as 'enhanced recovery after surgery' (ERAS) has been developed. The main pillars of ERAS programs include optimal postoperative pain management and early enteral feeding and mobilization after surgery. Several studies, mostly based on experiences with patients undergoing colonic resection, suggest that ERAS implementation is feasible and safe. However, there are very few well-designed studies that have evaluated the usefulness of ERAS programs after major upper abdominal surgery. The present review focuses on the discussion of the most relevant and recently published data on the application of ERAS programs in pancreatic, hepatic, esophageal and gastric surgery. A total of 23 articles have been reviewed by the authors. The high frequency and the potentially hazardous nature of some postoperative complications associated with major upper ab-

dominal surgery and the lack of well-designed randomized controlled trials are limiting factors for the application of ERAS. However, the present results indicate that the implementation of ERAS programs in pancreatic, hepatic, esophageal and gastric surgery patients contributes to a reduction in complications, length of hospital stay and costs without an increase in mortality or readmission rates.

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## Introduction

Over the last 20 years, a new concept of perioperative patient care after different types of surgical abdominal procedures has been developed and evaluated [1, 2]. This construct of evidence-based interventions, referred to as 'fast-track surgery', 'enhanced recovery after surgery' (ERAS) or 'multimodal rehabilitation', is mainly focused on the minimization of the impact of surgery on patients' homeostasis [3–5]. The reduction of postoperative physiological stress by attenuation of the neurohormonal response to the surgical intervention not only provides the basis for a faster recovery but also seems to diminish the risk of organ dysfunction and complications [1, 2]. There-



**Fig. 1.** Main perioperative components typically included in ERAS programs. Adapted from Varadhan et al. [6].

fore, the main goal of ERAS programs is to achieve a shorter hospital stay without increasing postoperative complications and readmission rates.

ERAS programs consist of well-organized ‘pathways’ of consecutive clinical interventions that begin from outpatient preoperative information, counseling and physical optimization, proceed through pre-, intra- and postoperative protocolled intrahospital actions and end with patient discharge following pre-established criteria [6]. The 3 main pillars of this organized structure are optimal postoperative pain management, early enteral feeding and aggressive rehabilitation/early mobilization after surgery [4, 6–10]. Figure 1 depicts the key elements included in a typical ERAS protocol, the heterogeneity of which usually requires a multidisciplinary collaboration involving anesthesiologists, surgeons, surgical nurses and physiotherapists [1].

Several studies have recently shown that ERAS programs could also reduce health care costs and are safe [11–15]. However, most of these studies were focused on colonic surgery patients, and there is little information on the usefulness of ERAS programs in patients undergoing major upper abdominal procedures.

The present nonsystematic review was conducted to discuss the findings of the most relevant and recent studies of ERAS programs applied to the field of pancreatic, hepatic, esophageal and gastric surgery.

## Search Strategy

Studies were identified from the Medline and Embase databases. The literature search included journal articles published up until January 31, 2013. Both MeSH terms and words contained in the ‘Title’ or ‘Title/Abstract’ were used. These included: liver/hepatic resection/surgery, pancreatic resection/surgery, pancreatotomy, gastric resection/surgery, gastrectomy, esophageal resection/surgery, esophagectomy, fast track, enhanced recovery after surgery, ERAS, clinical pathway and multimodal rehabilitation. All documents retrieved were restricted to full-length articles written in English or Spanish. To be eligible for review, the articles had to be clinical human studies and include the evaluation of at least 3 of the following ERAS items: preadmission counseling, intraoperative fluid restriction, analgesia program, avoidance or early removal of drains, avoidance or early removal of nasogastric tube, early oral intake, early mobilization and early discharge criteria. Furthermore, studies had to report at least 2 of the following outcome measures: length of intensive care unit (ICU) stay, postoperative complications, postoperative mortality, length of hospital stay, failed fast tracking, readmission rate and charges.

**Table 1.** Background data of the studies evaluating the use of ERAS programs in patients undergoing pancreatic and hepatic surgery

First author	Year	Type of operation	Study design	Number of patients
<i>Pancreas</i>				
Porter [16]	2000	PD or TP	prospective vs. historical cohort	80 vs. 68
Wichmann [17]	2006	pancreatic resection	case-control study	12 vs. 12
Berberat [18]	2007	pancreatic resection	prospective cohort	255
Kennedy [19]	2007	PD	prospective vs. historical cohort	91 vs. 44
Balzano [20]	2008	PD	retrospective vs. historical cohort	252 vs. 252
Kennedy [21]	2009	DP	retrospective vs. historical cohort	71 vs. 40
Montiel Casado [22]	2010	PD	retrospective cohort	82
di Sebastiano [23]	2011	pancreatic resection	prospective cohort	145
<i>Liver</i>				
MacKay [26]	2008	liver resection for CRLM	prospective cohort	12
van Dam [27]	2008	liver resection	prospective vs. historical cohort	61 vs. 100
Stoot [28]	2009	laparoscopic liver resection	prospective vs. historical or nonrandomized cohort	13 vs. 13
Lin [29]	2011	liver resection	prospective vs. historical cohort	56 vs. 61

PD = Pancreatoduodenectomy; TP = total pancreatectomy; DP = distal pancreatectomy; CRLM = colorectal liver metastasis.

### Pancreatic Resection

We found 8 articles that evaluated the results of the implementation of ERAS programs after pancreatic surgery [16–23] (table 1). None of the studies was a prospective randomized trial. There were 4 prospective clinical series compared with historical controls [16, 19–21], 1 case-control study [17], 2 prospective studies without a control group [18, 23] and 1 retrospective study [22]. Four studies referred to the management of patients after pancreatoduodenectomy procedures, 3 studies included different types of pancreatic resection, and in a single study, only distal pancreatectomy was assessed. As shown in table 2, all studies evaluated a pre-established postoperative pathway, which always included at least 1 or more actions related to the 3 main components of ERAS protocols, i.e. (1) optimal pain management (postoperative pain protocols, regional anesthesia, patient-controlled analgesia), (2) early enteral feeding (early oral progressive intake, early removal of nasogastric tube) and (3) aggressive rehabilitation (early and protocolled mobilization after surgery, respiratory physiotherapy, etc.). In 2 articles, the components of the clinical pathway were not reported [16, 22].

Results of the use of ERAS protocols are summarized in table 3. All studies showed that ERAS programs after pancreatic resections were feasible and safe, could be implemented in a short period of time and provided high-

quality care and a reduction of costs. The decrease in postoperative hospital stay achieved in these studies was not associated with an increase in morbidity, mortality or readmission rates, demonstrating the safety of their use in high-risk surgical patients.

### Liver Resection

Although mortality rates after surgery of the liver have decreased to 3–5% due to advances in operative techniques, surgical device technology and perioperative care, morbidity rates in large series of patients still remain high at between 30 and 45% [24, 25]. The high frequency and the potential severity of some of these complications, such as hemorrhage, transient liver failure and biliary leaks, are important considerations when changing standard postoperative care (e.g. routine use of intra-abdominal drains and nasogastric tubes) in favor of new, evidence-based, postoperative care protocols [5].

A total of 4 articles evaluated the impact of different types of ERAS protocols in liver surgery [26–29] (table 1). None of the reviewed articles was a randomized clinical trial. van Dam et al. [27] and Lin et al. [29] analyzed the results of 2 midsize prospective series, with 61 and 56 patients, respectively, as compared with historical controls. Both the Dutch and the Chinese groups used standardized clinical pathways which included the main ERAS

**Table 2.** ERAS components evaluated in the reviewed studies on pancreatic and liver surgery

First author	Preadmission counseling	Intraoperative fluid restriction	Analgesia program	Avoidance/early removal of drains	Avoidance/early removal of NGT	Early oral intake	Early mobilization	Early discharge criteria
<i>Pancreas</i>								
Porter [16]				√	√	√		
Wichmann [17]		√	√ <sup>a</sup>	√		√	√	
Berberat [18]			√	√	√	√		
Kennedy [19]	√		√	√	√	√	√	
Balzano [20]	√	√	√ <sup>a</sup>	√	√	√	√	√
Kennedy [21]	√		√	√	√	√	√	
Montiel Casado [22]	√		√ <sup>a</sup>		√	√	√	
di Sebastiano [23]		√	√		√	√	√	√
<i>Liver</i>								
MacKay [26]			√	√	√	√	√	
van Dam [27]		√	√ <sup>a</sup>	√	√	√	√	√
Stoot [28]	√	√	√ <sup>a</sup>		√	√	√	
Lin [29]	√		√ <sup>a</sup>	√	√	√	√	

NGT = Nasogastric tube.

<sup>a</sup> Use of spinal analgesia as part of the pain control program.

items, such as pain control protocols and early diet/mobilization programs (table 2). As shown in table 3, both studies showed a significant reduction in the length of hospital stay without an increase in mortality, morbidity or readmission rates. In another multicenter Dutch study, Stoot et al. [28] compared the implementation of an ERAS protocol with historical and nonhistorical controls. This small series of laparoscopic liver resections confirmed the safety of enhanced recovery programs (table 3). The initial results of a fast-track program used in 12 patients by MacKay and O'Dwyer [26] also confirmed its feasibility, with no mortality and acceptable morbidity rates (table 3).

### Esophageal Resection

Zehr et al. [30] in 1998 showed that standardized clinical care pathways could reduce the length of hospital stay and costs in patients undergoing esophagectomies. Specific perioperative interventions, such as intraoperative fluid restriction, early extubation, effective pain management and early mobilization and nutrition, have been progressively incorporated into the new fast-track protocols (tables 4, 5). Two early studies evaluated effective pain control and conservative intraoperative fluid administration as main targets to reduce complications and to improve postoperative recovery [31, 32]. Brodner et al.

[31] prospectively evaluated ERAS in 49 patients undergoing esophagectomy, in whom ERAS consisted of effective intraoperative thoracic epidural analgesia, patient-controlled postoperative epidural analgesia with continuous evaluation and treatment by an acute pain service, early tracheal extubation and early mobilization of the patients. When compared with a previous cohort of patients undergoing the same operative procedure before the implementation of ERAS, patients in the prospective group regained gut function earlier and showed less catabolism, rapid efficient spontaneous ventilation and a shorter stay in the ICU (table 6). Neal et al. [32] prospectively evaluated 56 consecutive patients who underwent esophagectomy at a high-volume center, focusing on the following 2 perioperative aspects: intraoperative fluid restriction and extubation before leaving the operating room combined with thoracic epidural analgesia supervised by an acute pain service (table 6). Overall morbidity was 18%, with no instances of respiratory failure. A further study from the same group confirmed their previous excellent results in a larger series of patients managed postoperatively with an evolving standardized clinical pathway [33] (table 6). Immediate extubation was achieved in all patients. Also, virtually all patients had patient-controlled epidural analgesia. The incidence of pulmonary complications remained lower than 20%, and the 90-day mortality rate was 0.33% (table 6).

**Table 3.** Results of ERAS program implementation in pancreatic and hepatic cancer surgery and differences compared to control groups (when present)

First author	Postoperative complications, %	Mortality, %	Length of hospital stay, days	Readmission rate, %	Hospital charges USD × 10 <sup>3</sup>
<i>Pancreas</i>					
Porter [16]	30 vs. 29 <sup>a</sup>	1.2 vs. 2.9	13.5 vs. 16.4*	11.2 vs. 14.7	36.6 vs. 47.5*
Wichmann [17]	8.3 vs. 8.3	NA	12.9 vs. 20	NA	NA
Berberat [18]	surgical: 24.7 medical: 16.5	2	10	3.5	NA
Kennedy [19]	37 vs. 44	1.1 vs. 2.3	7 vs. 13*	7.7 vs. 7	126.5 vs. 240.2
Balzano [20]	14 vs. 25*	3.6 vs. 2.8	11 vs. 13*	7 vs. 6	NA
Kennedy [21]	37.5 vs. 15.5	1.1 vs. 2.3	6.7 vs. 10.2*	7 vs. 25*	22.8 vs. 26.3
Montiel Casado [22]	47.6	4.9	9	14.6	NA
di Sebastiano [23]	38.6	2.7	10	6.2	NA
<i>Liver</i>					
MacKay [26]	25	0	4	NA	NA
van Dam [27]	40.9 vs. 31	0 vs. 2	6 vs. 8*	13.1 vs. 10	NA
Stoot [28]	15.3 vs. 15.3	0 vs. 0	5 vs. 7	0 vs. 0	NA
Lin [29]	46.4 vs. 44.3	1.8 vs. 1.6	7 vs. 11*	7.1 vs. 3.3	3 vs. 3.8*

When a control group is present, results are expressed as ERAS vs. no ERAS. \*  $p < 0.05$ : statistical significance between study groups. NA = Data not available.

<sup>a</sup> Only major complications are shown.

**Table 4.** Studies assessing ERAS components for patients undergoing esophageal and gastric resections

First author	Year	Type of operation	Study design	Number of patients
<i>Esophagus</i>				
Brodner [31]	1998	abdominothoracic ER	prospective vs. historical cohort	42 vs. 49
Neal [32]	2003	abdominothoracic ER	prospective cohort	56
Cerfolio [34]	2004	abdominothoracic ER <sup>a</sup>	prospective cohort	90
Low [33]	2007	abdominothoracic ER	prospective cohort	340
Jiang [35]	2009	abdominothoracic ER	prospective cohort	114
Munitiz [36]	2010	abdominothoracic ER <sup>a</sup>	prospective vs. historical cohort	74 vs. 74
Preston [37]	2013	abdominothoracic ER	prospective vs. historical cohort	12 vs. 12
<i>Stomach</i>				
Grantcharov [39]	2010	laparoscopic gastrectomy	prospective cohort	32
Wang [40]	2010	open gastrectomy	RCT	45 vs. 47
Liu [41]	2010	open gastrectomy	RCT	33 vs. 30
Yamada [42]	2012	open and laparoscopic gastrectomy	prospective vs. historical cohort	91 vs. 100
Chen Hu [43]	2012	open gastrectomy laparoscopic gastrectomy	RCT	19 vs. 22 21 vs. 21

ER = Esophageal resection; RCT = randomized clinical trial.

<sup>a</sup> Ivor Lewis operation.

**Table 5.** ERAS components evaluated in the reviewed studies on esophageal and gastric resections

First author	Preadmission counseling	Intraoperative fluid restriction	Thoracic epidural analgesia	Early extubation	Avoidance/early removal of drains	Avoidance/early removal of NGT	Early enteral/oral feeding	Early mobilization	Early discharge criteria
<i>Esophagus</i>									
Brodner [31]			√ <sup>a</sup>	√				√	
Neal [32]		√	√ <sup>a</sup>	√			√ <sup>b</sup>	√	√
Cerfolio [34]	√		√	√	√	√	√ <sup>b</sup>	√	√
Low [33]	√	√	√ <sup>a</sup>	√	√	√	√ <sup>b</sup>	√	√
Jiang [35]	√			√	√	√	√ <sup>b</sup>	√	√
Munitiz [36]			√	√	√	√	√	√	√
Preston [37]	√	√	√	√	√	√	√ <sup>b</sup>	√	
<i>Stomach</i>									
Grantcharov [39]	√				√	√	√	√	√
Wang [40]	√	√	√		√	√	√	√	√
Liu [41]	√				√	√	√	√	√
Yamada [42]			√		√	√	√	√	√
Chen Hu [43]	√	√			√	√	√	√	√

Early extubation was specifically assessed in esophagectomy trials. NGT = Nasogastric tube.

<sup>a</sup> Thoracic epidural analgesia with continuous evaluation by an acute pain service.

<sup>b</sup> Early start of postoperative enteral nutrition before oral intake.

**Table 6.** Results of ERAS program implementation in esophageal and gastric cancer surgery and differences compared to control groups (when present)

First author	ICU stay days	Postoperative complications, %	Mortality %	Hospital stay, days	Failed fast-tracking, %	Readmission rate, %	Hospital charges USD × 10 <sup>3</sup>
<i>Esophagus</i>							
Brodner [31]	1.7 vs. 4.0*	NA	0 vs. 10.2	NA	NA	NA	NA
Neal [32]	1	18	0	10	NA	NA	NA
Cerfolio [34]	1	26.6	4.4	7	22	4.4	NA
Low [33]	2.2	45	0.3	11.5	14 <sup>a</sup>	NA	NA
Jiang [35]	NA	16.6	2.6	7	22.8	4	NA
Munitiz [36]	NA	31 vs. 38	1 vs. 5	9 vs. 13	31	4.5	NA
Preston [37]	3 vs. 4*	33 vs. 75*	0 vs. 0	7 vs. 17*	NA	NA	NA
<i>Stomach</i>							
Grantcharov [39]		6.2 <sup>b</sup>	0	4	NA	6.2	NA
Wang [40]		20 vs. 14.9	0 vs. 0	6 vs. 8*	NA	2.2 vs. 2.1	4.3 vs. 4.9*
Liu [41]		12.1 vs. 20	0 vs. 0	6.2 vs. 9.8*	NA	3 vs. 0	NA
Yamada [42]		7.6 vs. 12 <sup>b</sup>	0 vs. 0	9 vs. 9	5.5	NA	NA
Chen Hu [43]							
Open		23.8 vs. 15 <sup>b</sup>	0 vs. 0	7.5 vs. 8.75*	NA	NA	4.4 vs. 4.6*
Laparoscopic		26.3 vs. 18.2 <sup>b</sup>	0 vs. 0	7 vs. 7.5			5.3 vs. 5.7*

When a control group is present, results are expressed as ERAS vs. no ERAS. ICU stay was specifically assessed in esophagectomy trials. \*  $p < 0.05$ : statistical significance between study groups. NA = Data not available.

<sup>a</sup> Postoperative day 1 mobilization was not achieved as scheduled.

<sup>b</sup> Only major complications are shown.



A more structured fast-tracking pathway following esophageal resection (Ivor Lewis operation) was first reported in 2004 by Cerfolio et al. [34], with the primary objective to accelerate postoperative recovery and reduce hospital stay to 7 days while maintaining safety and patient satisfaction (table 6). The fast-track protocol could be applied in 77% of the patients, and these patients were discharged home by postoperative day 7 without compromising morbidity, mortality or patient satisfaction. Patients who were older than 70 years or who had undergone neoadjuvant therapies were more likely to have postoperative complications and thus were less likely to tolerate measures of the fast-tracking protocol. Jiang et al. [35] reported a similar median length of hospital stay of 7 days in a series of 114 patients undergoing abdominothoracic esophagectomy with the use of a fast-track protocol (table 6). Patients under 65 years of age or without preoperative underlying disorders fared better on the proposed fast-track targets. Munitiz et al. [36] confirmed the ability of a standardized clinical care pathway to reduce pulmonary complications and shorten hospital stay by comparing a group of 74 patients undergoing Ivor Lewis esophagogastrectomy with a previous cohort of patients who had the same operation without a fast-track protocol (table 6). As reported in the 2 previous studies [33–35], failed fast-tracking was more common among patients aged over 70 years and those who received neoadjuvant treatments.

More recently, Preston et al. [37] demonstrated improvements in short-term outcomes after esophagectomy following the adoption of an established standardized postoperative pathway [33]. An increase in the rate of immediate extubation and in the proportion of patients mobilizing on the first postoperative day was achieved, and there were subsequent significant reductions in postoperative complication rates, as well as shorter critical care and overall hospital stay [37]. The authors recognized the small number of patients included in both study groups as the main limitation of their study.

Factors that delay recovery and influence the length of hospital stay after esophagectomy include pain control, respiratory care, anastomotic healing and subsequent oral alimentation [30]. Based on previous data, standardized clinical pathways can provide the basis to set perioperative goals ('fast-tracking') such as fluid restriction, early extubation, continuous thoracic epidural analgesia supervised by a pain service and early mobilization, which improve postoperative outcomes in patients undergoing this technically complex and high-risk operation [38].

Specific interventions such as those described previously also reduce ICU length of stay as well as the rate of respiratory complications, all of which translate into a shorter hospital stay. The combination of ERAS and minimally invasive surgery needs to be evaluated in the future.

### Gastric Resection

Three randomized controlled trials and 2 prospective cohort studies evaluated open and minimally invasive gastrectomy combined with fast-track principles of perioperative care, mainly in the setting of cancer patients (tables 4, 5). Grantcharov and Kehlet [39] showed that laparoscopic gastrectomy combined with fast-track components of perioperative care (table 5) resulted in a short hospital stay (4 days) and low morbidity rate. Two randomized trials from China showed that fast-track surgery accelerates rehabilitation in patients undergoing open gastric resection [40, 41] (table 6). Readmission rates in both studies were lower than 5%. Yamada et al. [42] prospectively evaluated an ERAS protocol in 91 patients undergoing open or laparoscopic gastrectomy (total and distal) and compared early postoperative outcomes with those from a previous cohort of patients undergoing the same operation and following a conventional perioperative care protocol. The ERAS group achieved earlier oral intake, flatus and defecation, but the duration of postoperative stay was similar in both study groups, which was attributed to the particular discharge criteria of the hospital. More recently, Chen Hu et al. [43] reported a randomized controlled trial including 4 groups (laparoscopic distal gastrectomy, fast-track plus laparoscopic distal gastrectomy, open distal gastrectomy and fast-track plus open distal gastrectomy). Except for the open gastrectomy group, all groups had a similar duration of postoperative hospital stay. The fast-track open gastrectomy group had the lowest medical cost. These results suggest that fast-track surgery was safe, feasible and efficient.

### Discussion

One important issue that emerges from this review is the lack of standardization of the clinical pathways implemented in the different studies. Most of the ERAS programs incorporate the main items of multimodal rehabilitation, such as postoperative pain management, early oral feeding and early mobilization. However, it should be noted that every surgical group designed its own clin-

ical pathway and decided which items of ERAS programs should be included in the protocol. Moreover, several interventions were developed in different ways. For example, in relation to postoperative pain management, only 14 of the 23 groups included thoracic epidural analgesia; in addition, different postoperative pain control protocols were used. Early oral intake was implemented by almost all groups as a part of the ERAS program, but in the majority of studies the type of diet was not reported. Finally, early mobilization was introduced in 21 studies, although the mode of mobilization varied from sitting in a chair to an aggressive postoperative rehabilitation schedule. Other important components of ERAS programs, such as preadmission counseling, goal-directed intraoperative fluid management or early discharge criteria, were only sporadically mentioned as part of the analyzed protocols. This lack of standardization makes it very difficult to compare the results among different studies and reduces the possibility of extending the implementation of enhanced recovery programs to other centers. In this respect, development of local or national guidelines which specifically describe the ERAS items that should be included in postoperative protocols is highly desirable. Moreover, it would be important to differentiate protocols based on specific surgical operations and previous performance status of the patient.

The advent of minimally invasive surgery in pancreatic, hepatic, esophageal and gastric resections implies a change in postoperative patient management. The need for some ERAS components, such as spinal analgesia, respiratory rehabilitation or prolonged antithrombotic prophylaxis, may be reduced after laparoscopic surgery, except for certain high-risk patients. Clearly, advances in the surgical techniques should imply an evolution in the postoperative management of the patient.

The results of 3 studies on ERAS implementation after esophageal surgery [33, 35, 36] suggest that patients' compliance to postoperative rehabilitation protocols is deeply influenced by age and other clinical variables, including the use of neoadjuvant therapy. Thus, it seems reasonable to 'personalize' postoperative pathways based on a stratification of patients which could include age, previous illness, performance status and oncologic treatment. Furthermore, we believe that future studies should always include data on patient compliance to ERAS pathways, which is an extremely important feedback about the applicability of these concepts to high-risk and fragile patients.

The difficulty of performing well-designed randomized clinical studies supporting the feasibility and safety

of ERAS programs has been described previously by other authors [1, 27] and is confirmed by the present review, in which only 3 of the selected studies were randomized controlled trials. A possible solution to this problem, as described by Kehlet and Wilmore [1], may be to obtain additional evidence from multi-institutional series using the same standardized fast-track approaches for the same surgical procedures and with well-described patient demographics in order to compare these results with traditional care provided during the same time period.

## Conclusion

In conclusion, the results of the present nonsystematic review suggest that the implementation of ERAS programs after major upper abdominal surgery is feasible and safe, achieving a decrease in postoperative hospital stay and, in some cases, in postoperative complications and hospital costs, without an increase in mortality or readmission rates. However, these promising results should be confirmed in well-designed clinical trials using standardized ERAS protocols.

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## Disclosure Statement

None of the authors have financial conflicts of interest to declare.

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