



Enhanced recovery after surgery for gastric cancer (ERAS-GC): optimizing patient outcome

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Abstract: Significant advances were achieved, in last decades, in the management of surgical patients with gastric cancer. This has led to the concept of enhanced recovery after surgery (ERAS) with the objective of reducing the length of hospital stay, accelerating postoperative recovery and reducing the surgical stress. The ERAS protocols have many items, including the pre-operative patient education, early mobilization and feeding starting from the first postoperative day. This review aims to highlight possible advantages on postoperative functional recovery outcomes after gastrectomy in patients undergoing an ERAS program, current lack of evidences and future perspectives.

Keywords: Enhanced recovery after surgery (ERAS); gastric cancer; gastrectomy

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Introduction

In Europe, the end of the 1990s saw the development of a multidisciplinary approach for cancer patients undergoing surgery, particularly in the case of colorectal cancer. The objective was to reduce the surgical stress on the patient and at the same time reduce the cost of hospitalization (1). Different strategies have been proposed under various names, including fast-track surgery, enhanced recovery program, accelerated rehabilitation care, and enforced multimodal rehabilitation care.

Given the growing interest in this field, especially in the West, a specific study group was organized in the context of the European Society of Clinical Nutrition and Metabolism (ESPEN) in 2001. The term enhanced recovery after surgery (ERAS) came into usage for the first time in 2002. Later, in 2009, emerging data from preliminary studies guided the issuance of the first consensus guidelines (2). Soon, principles first adopted in colorectal surgery became more commonly applied in other procedures. However, specific ERAS guidelines for gastric cancer were not published until 2014 (ERAS-GC) (3). Consequently, the

literature has little to offer regarding institutions that have adopted an ERAS-GC protocol. In addition, while evidence has been growing in recent years, results are difficult to generalize due to differences in patient characteristics, disease extension, and health systems.

Table 1 summarizes the randomized studies published from the issuing of the ERAS Society guidelines (4-9).

The ERAS-GC guidelines consist of two sections. The first includes general enhanced recovery items that coincide with the guidelines for pancreaticoduodenectomy (10), while the procedure-specific guidelines contain eight elements (3): preoperative nutrition, preoperative oral pharmaconutrition, access, wound catheters and transversus abdominis plane block, nasogastric/nasojejunal decompression, perianastomotic drains, early postoperative diet and artificial nutrition, and audit. This review offers an analysis of the principles and future perspectives of the ERAS-GC program.

Preoperative nutrition

A recent study, exploring the effects of preoperative nutrition

Table 1 Characteristics of current Randomized controlled trials, published since the introduction of the ERAS guidelines for gastrectomy

Author	Year	Language	Approach	ERAS group (No.)	Control group (No.)	Type of surgery	Main outcomes reported
Wang (4)	2014	Chinese	Open	71	71	NR	LHS, RBF, HC
Abdikarim (5)	2015	English	Laparoscopy	30	31	DG, TG	LHS, C, RBF
Bu (6)	2015	English	Open	128	128	DG, TG	LHS, C, R, RBF, HC
Liu (7)	2016	English	Open/laparoscopy	42	42	DG, TG	LHS, C, RBF, HC
Mingjie (8)	2016	English	Open	73	76	NR	LHS, C, RBF
Kang (9)	2018	English	Laparoscopy	46	51	DG	LHS, C, M, R, RBF

LHS, length of hospital stay; C, complications; M, mortality; R, readmission; RBF, return of bowel function; HC, hospital cost; DG, distal gastrectomy; TG, total gastrectomy; NR, not reported; ERAS, enhanced recovery after surgery.

in patients with gastric cancer, showed a direct correlation for both short-term (risk of infection) and long-term survival and disease recovery (11). This finding highlights that adequate nutrition, commencing immediately at the start of the perioperative period, has a considerable impact that cannot be overlooked. In comparison, the guidelines suggest the need to identify patients suffering malnutrition and to determine its severity (3). That said, routine preoperative parenteral nutrition is not recommended in the absence of specific needs.

More recently, randomized trials (12-14) have introduced the concept of immune nutrition, aiming to modulate the systemic inflammatory response. In particular, researchers have found that omega-3 fatty acid and arginine reduce the duration of systemic inflammatory response syndrome and the incidence of infectious postoperative complications (12). Mochiki (13) also described the effect of glutamine on the recovery of intestinal motility. Three reviews and meta-analyses (15-17) related to immunonutrition confirmed that perioperative nutritional support is effective for improving patient immunity and modulating the inflammatory response; however, evidence is lacking concerning the modalities, timing, and characteristics of patients that can receive the most benefit as well as product formulations.

Minimally invasive surgery

The ERAS guidelines (3) recommend the use of minimal-access surgery in order to facilitate short incisions, resulting in less trauma to the tissues. However, in gastric surgery, albeit the use of laparoscopy and robotic surgery is spreading in referral centers, significant debate continues regarding the use of these approaches for advanced gastric cancer (AGC). As another factor in the discussion, AGC

represents the majority of patients undergoing surgery in Western countries. Although some authors have published the results of ERAS-GC with open access, minimally invasive surgery represents a fundamental element for the success of an ERAS-based program as it provides support for guaranteeing reduced stress to tissue and rapid physiological recovery.

Authors of systematic reviews and meta-analyses have attempted to define the role of minimally invasive surgery (laparoscopy, robotic surgery, hybrid procedures) for gastric cancer by comparing it with the open approach (18-20). The guidelines describe laparoscopy as a possible alternative to open surgery for early gastric cancer (21); meanwhile, robotic surgery possesses intrinsic technological advantages as articulated instruments may be comfortably controlled from a remote console while offering a 3D view.

Several issues are currently subject to debate in gastric cancer (22,23). Most important is ensuring proper oncological surgery by performing an adequate lymphadenectomy. In randomized trials (19), laparoscopy demonstrated the removal of an adequate number of lymph nodes as required by international guidelines (21).

As another factor, robotic surgery can facilitate better D2 dissection. Advanced technology clearly offers intrinsic advantages for this surgical step, but researchers have not yet proven and verified these through appropriate trials: only four studies (24-27) have contrasted robotic surgery with the open approach, and only one study showed a statistically significant difference in comparison to laparoscopy (28).

Among the intraoperative outcomes, most of the available studies found that minimally invasive surgery led to reduced blood loss. This finding achieved high statistical significance for laparoscopy in Vinueza's meta-analysis of

RCTs (19). Meanwhile, with regard to robotic surgery, a general consensus among different studies has described some advantages over laparoscopy and open surgery in reducing operative bleeding (28,29). Several studies, however, have also reported conflicting results (30,31).

Regarding the post-operative period, the largest RCT (32), performed by the Korean Laparoscopic Gastrointestinal Surgery Study Group, found no significant difference between laparoscopy and open surgery concerning overall complications. In contrast, other studies have shown a significant reduction in medical and minor surgical complications when using laparoscopy (19). Moreover, researchers' findings have been inconsistent in studies examining robotic surgery when attempting to demonstrate differences compared to laparoscopy in terms of analyzing complications (24,30,33).

Overall, despite the extreme heterogeneity among studies, minimally invasive surgery has demonstrated relevant advantages when compared with open surgery in the area of postoperative hospital stays (20). Some evidence has indicated that patients who underwent robotic gastrectomy could be discharged at an earlier date than patients who underwent open or laparoscopic gastrectomy (34,35). However, the low number of studies in this field along with high heterogeneity weaken this conclusion.

Manually handling organs during surgery is an important contributor to the inflammatory response after surgery (36). Thus, the smaller minimally invasive instruments may cause less inflammation than the instruments used in open surgery.

Nasogastric/nasojejunal decompression

Studies (37,38) concur that the nasogastric/nasojejunal tube should not be used routinely in subjects eligible for the ERAS-GC protocol. The literature has reported no advantage from its routine use (5). In fact, those studies (37,38) have shown that use of the nasogastric tube does not reduce the risk of anastomotic leakage, the number of pulmonary complications, or mortality; in addition, such use significantly reduces the patient's post-operative comfort. Furthermore, in Yang's meta-analysis (39), the authors showed that postoperative tube maintenance prolongs postoperative ileus and time to the first flatus. Yamada (40) also reported that complications potentially caused by a shortening of the postoperative fasting period, such as atelectasis pneumonia or anastomotic leakage, do not increase under the ERAS protocol.

Perianastomotic drains

The guidelines recommend avoiding the use of abdominal drainage to reduce related complications and accelerate patient recovery (3); however, the level of evidence is low, and only a few cases have been analyzed in a recent meta-analysis of the Cochrane Library (41).

In any event, the absence of abdominal drainage is an additional factor that improves patient comfort as well as stimulates and facilitates walking. While the scientific evidence does not show any benefit in the use of abdominal drainage for numerous surgical procedures (42,43), in the case of gastric surgery, little evidence is available. In particular, the use of drainage after total gastrectomy is still widely debated in the context of the ERAS programs. Therefore, caution is necessary in this case, particularly after extensive lymphadenectomy.

Mobilization

A fundamental item in the ERAS protocol (3) is early mobilization, which is facilitated by the absence of the nasogastric tube and drainage as well as by early removal of the urinary catheter. Smart (44) showed that failure to mobilize patients early is significantly associated with a lengthening of post-operative hospitalization. Many studies (35,40,45,46) have shown that the application of this item of the ERAS program can significantly accelerate the recovery of post-operative intestinal function in comparison to a group subjected to conventional management.

Early postoperative diet

The ERAS protocols require that the patient should not be subjected to long periods of fasting. It has been amply demonstrated that early nutrition reduces postoperative catabolism, accelerates the return of intestinal function, and reduces the risk of complications (47,48). Furthermore, Lewis *et al.* (49) confirmed in their meta-analysis that keeping patients fasted does not yield any benefit. In fact, although the topic remains controversial, several studies (46,50) have shown that early oral nutrition is not only feasible in gastric surgery but brings significant benefits. Despite the fact that an early dietary recovery has been shown to speed up the patient's recovery after several surgical procedures, concerns (actually unfounded) related to possible correlation with higher risk of anastomotic leakage or bowel obstruction have caused this approach

following gastrectomy to be viewed with distrust. Recent studies (40,51) have confirmed that early feeding after gastrectomy is safe and associated with an improvement in functional recovery and a reduction in hospital stay.

In particular, a randomized controlled trial (52) reported safety data on oral feeding resumption from the second postoperative day after gastrectomy. Studies by Makuuchi (53) and Pedziwiatr (54), comparing the adoption of an ERAS protocol versus conventional management after gastrectomy, confirmed the observation that the recovery of oral nutrition is safe from the second postoperative day. This practice was also found to correlate with a reduction in post-operative administration of intravenous fluids and early discharge (55).

In comparison, Sugisawa (56) focused on evaluating the rate of anastomotic leakage and ab-ingestis pneumonia to assess the real risk attributable to early nutrition. In this study (56), the incidence of anastomotic leakage was 0.8% in the ERAS group, a value not only lower than that of its historical comparison cohort (1.7%) but also in line with or lower than the data rendered by previous studies reporting conventional perioperative management (0.8–1.9%). Therefore, the author concluded that early oral nutrition does not negatively affect the anastomotic site. Yamada (40,57) obtained results that revealed a similar incidence in the rate of leakage (1.1%).

On this topic, the guidelines (3) do not clearly state the different steps to take in resuming oral intake after gastrectomy, but they support an early administration of oral liquids from the first postoperative day. For those patients who are unable to reach at least 60% of the required caloric intake, a tailored nutritional support is recommended. This item, however, is much debated: some authors (58) underline the difficulty in developing specific protocols due to considerable differences regarding type of gastrectomy, stage of disease, and the general condition of the patient.

Perspectives

The effects of adopting an ERAS-GC program depend not only on clinical factors but also on health systems and the socio-cultural substrate of patients. For example, Yamada (40) reported that although ERAS patients had a more rapid functional recovery than those in the conventional group, the length of hospital stay did not differ significantly between the two groups. The authors attributed this result primarily to the Japanese Diagnosis

Procedure Combination-based Payment System (DPC) that allows patients to extend their stay at a reduced cost. Among others, Sugisawa (56) reported that the median postoperative hospital stay was significantly reduced in the ERAS group (8 days) compared to its historical cohort (10 days; $P=0.001$). Wang (46) obtained similar results.

Regarding post-operative complications and the need for reoperations, all studies (35,40,53,56) confirmed the safety of the ERAS approach. Furthermore, they identified no statistically significant difference between the experimental and control groups.

Since the publication of the ERAS-GC guidelines, four meta-analyses (59–62) have been published. Li (61) showed that ERAS-GC with the laparoscopic approach allows a reduction in postoperative hospitalization and reduced costs due to faster recovery without an increase in the readmission rate or complications. In their study, Ding *et al.* (59) revealed that ERAS improves the postoperative inflammatory response. In addition, Wang (62) reported that ERAS quickens the recovery process with significant reduction in surgical stress and hospitalization costs in addition to improving the nutritional aspects and the quality of life of the patients.

While such evidence is prompting referral centers to adopt strategies, in the spirit of ERAS, to optimize the management of patients with gastric cancer, it is admittedly difficult to generalize the results. In the end, each institution, depending on its needs, should create its own patient-based pathways.

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Footnote

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