### **REVIEW ARTICLE**



# Current status of the "enhanced recovery after surgery" program in gastric cancer surgery

Yukinori Yamagata | Takaki Yoshikawa 💿 | Masahiro Yura | Sho Otsuki | Shinji Morita | Hitoshi Katai | Toshiro Nishida

Department of Gastric Surgery, National Cancer Center Hospital, Tokyo, Japan

#### Correspondence

Takaki Yoshikawa, Department of Gastric Surgery, National Cancer Center Hospital, Tokyo, Japan. Email: tayoshik@ncc.go.jp

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#### Abstract

Since the late 1990s, perioperative care through the enhanced recovery after surgery (ERAS, European Society for Clinical Nutrition and Metabolism [ESPEN]) program has spread. ERAS protocols aim to reduce surgical complications, improving postoperative outcomes and thereby saving resources by addressing various clinical elements through a multidisciplinary approach or based on evidence. In the field of gastric cancer, the philosophy of ERAS has gradually become accepted and, in 2014, consensus guidelines for enhanced recovery after gastrectomy were published. These guidelines consist of "procedure-specific" guidelines and "general (not procedure-specific) enhanced recovery items." In this review, we focused on the procedure-specific guidelines and tried to update the contents of every element of the procedure-specific guidelines. The procedurespecific guidelines consist of the following eight elements: "Preoperative nutrition," "Preoperative oral pharmaconutrition," "Access (of gastrectomy)," "Wound catheters and transversus abdominis plane block," "Nasogastric/Nasojejunal decompression," "Perianastomotic drains," "Early postoperative diet and artificial nutrition," and "Audit." On reviewing papers supporting these elements, it was reconfirmed that the recommendations of the guidelines are pertinent and valid. Four meta-analyses concerning the evaluation of ERAS protocols for gastric cancer were included in this review. Every study showed that the ERAS protocol reduced the cost and duration of hospital stay without increasing surgical complication rates, suggesting that ERAS is effective for gastric cancer surgery. However, it cannot be said that ERAS has achieved full penetration in Japan because most evidence is established in Western countries. Future studies must focus on developing a new ERAS protocols appropriate to Japanese conditions of gastric cancer.

#### KEYWORDS

ERAS, gastric cancer, meta-analysis, perioperative care, review

## 1 | INTRODUCTION

In Northern Europe in the late 1990s, a perioperative management program for patients with colorectal cancer was proposed. By addressing various clinical elements through a multidisciplinary approach or based on evidence, this program aimed to reduce surgical complications or surgical stress, strengthen resilience, shorten hospital stay, improve safety, and reduce costs.<sup>1</sup> This

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program gradually became popular in Europe, and a study group was organized within the European Society of Clinical Nutrition and Metabolism (ESPEN) in 2001, with the term "enhanced recovery after surgery (ERAS)" used for the first time at the 2002 ESPEN meeting. These series of ideas were summarized as consensus guidelines by the ERAS study group in 2009.<sup>2</sup>

Originally, the ERAS program was developed as a protocol for colorectal surgery, but the idea has been applied to other types of surgical procedures. In 2012, guidelines for colon surgery, rectal/ pelvic surgery, and pancreaticoduodenectomy were published by the ERAS study group.<sup>3-5</sup> The same group announced guidelines for gastric cancer surgery in 2014, and the idea of perioperative management by ERAS has since been gradually spreading.<sup>5</sup>

Principles of the ERAS protocol are as mentioned earlier, and there are many terms expressing similar concepts, such as fast track program/surgery, enforced multimodal rehabilitation program, enhanced recovery program, accelerated rehabilitation care, and so on. These concepts include many elements (Figure 1)<sup>1</sup> and differentiation of them is vague; hence, in the present review, we regarded every type of action beneficial to the patient as a part of ERAS.

In the present review, as it has now been 4 years since the ERAS guidelines for gastrectomy were announced, we decided to assess the penetration of the ERAS protocols among gastric cancer surgeons. In addition, since the papers cited in those guidelines are articles published from the 2000s to the early 2010s, we accumulated more recent evidence of several ERAS elements of gastrectomy in order to update the guidelines. When interpreting evidence of ERAS, differences in gastric cancer surgery must be taken into consideration. Between the Western countries and Japan, there may be huge differences in patient characteristics, extent of nodal dissection, quality of surgery, and even perioperative care before ERAS. Many Japanese surgeons may believe that perioperative care by ERAS is not applicable to the "Japanese style" of gastric cancer surgery. In this review, we collected evidence both from Western countries and from Japan, then considered applicability of evidence, and current status and future prospects of ERAS in Japan.

# 2 | CONSENSUS GUIDELINES FOR ENHANCED RECOVERY AFTER GASTRECTOMY

#### 2.1 | Concerning the guidelines

As mentioned above, the "Consensus guidelines for enhanced recovery after gastrectomy (the Guidelines)" were published by the ERAS study group in 2014.<sup>6</sup> The guidelines consist of two parts: "procedure-specific" guidelines and "General (not procedurespecific) enhanced recovery items." The latter is shared with the ERAS guidelines for pancreaticoduodenectomy.

Table 1 indicates Procedure-specific guidelines of consensus guidelines for enhanced recovery after gastrectomy. In the procedure-specific guidelines, the following eight elements are listed as elements specific to gastrectomy: "Preoperative nutrition," "Preoperative oral pharmaconutrition," "Access (of gastrectomy)," "Wound catheters and transversus abdominis plane block," "Nasogastric/Nasojejunal decompression," "Perianastomotic drains," "Early postoperative diet and artificial nutrition," and "Audit." In the present review, we focused on the elements "Preoperative nutrition/ pharmaconutrition," "Access of gastrectomy," "Nasogastric decompression," "Perianastomotic drains," and "Early postoperative diet and artificial nutrition," as these are elements in which surgeons tend to be particularly interested. We also mentioned new papers concerning these elements.

#### 2.2 | Preoperative nutrition/pharmaconutrition

Regarding preoperative nutrition/pharmaconutrition, the guidelines summarized that routine use of preoperative artificial nutrition is not warranted and the benefit of preoperative oral pharmaconutrition is controversial. However, the guidelines described the need to identify malnourished patients and to provide enteral feeding to these patients.<sup>6</sup> We found a prospective study regarding the effects of preoperative nutrition on patients with gastric cancer published in 2017,<sup>7</sup> and it showed a higher incision infection rate and lower



**FIGURE 1** Main elements of the enhanced recovery after surgery protocol.<sup>1</sup> NSAIDs, non-steroidal antiinflammatory drugs

**TABLE 1** Procedure-specific guidelines of consensus guidelines for enhanced recovery after gastrectomy (partially modified)<sup>6</sup>

	Summary and recommendation	Evidence level	Recommendation grade
Preoperative nutrition	Routine use of preoperative artificial nutrition is not warranted, but significantly malnourished patients should be optimized with oral supplements or enteral nutrition before surgery	Very low	Strong
Preoperative oral pharmaconutrition	Benefit shown for major gastrointestinal cancer surgery in general has not been reproduced in dedicated trials on patients undergoing gastrectomy. Although a benefit cannot be excluded, there is presently insufficient evidence for this patient group	Moderate	Weak
Access	Evidence supports LADG in early gastric cancer as it results in fewer complications, faster recovery and may be carried out to a standard that is oncologically equivalent to open surgery	High	Strong
	T2-T4a gastric cancer, more data on long-term survival comparing LADG and ODG are needed	Moderate	Weak
	There is some evidence supporting LATG owing to lower postopera- tive complications, shorter hospital stay and oncological safety. However, LATG is technically demanding	Moderate	Weak
Wound catheters and TAP block	Evidence is conflicting regarding wound catheters in abdominal surgery	Low to moderate	Weak
	Evidence is strong in support of TAP block in abdominal surgery, although the effect is evident only during the first 48 h after surgery and none of the evidence is from gastrectomies	Low	Weak
Nasogastric/nasojejunal decompression	Nasogastric tubes should not be used routinely	High	Strong
Perianastomotic drains	Avoiding the use of abdominal drains may reduce drain-related complications and shorten hospital stay after gastrectomy	High	Strong
Early postoperative diet	Patients undergoing total gastrectomy should be offered drink and food at will from POD 1. They should be advised to begin cautiously and increase intake according to tolerance	Moderate	Weak
And artificial nutrition	Patients clearly malnourished or those unable to meet 60% of daily requirements by POD 6 should be given individualized nutritional support	Moderate	Strong
Audit	Systematic audit improves compliance and clinical outcomes	Low	Strong

LADG, laparoscopy-assisted gastrectomy; LATG, laparoscopy-assisted total gastrectomy; ODG, open distal gastrectomy; POD, postoperative day; TAP, transversus abdominal plane.

3-year overall survival and disease-free survival in malnourished patients than in those receiving adequate nutrition. These findings suggest that efforts to manage preoperative malnutrition in patients with gastric cancer should be optimized, as the guidelines asserted.

Perioperative immunonutrition is a recent topic considered to have potential to modulate the systemic inflammatory response induced by surgical invasion. From Japan, three prospective randomized trials were published around 2010.<sup>8-10</sup> Okamoto et al<sup>8</sup> reported that preoperative arginine- and omega-3 fatty acid-supplemented immunonutrition reduced the duration of systemic inflammatory response syndrome (SIRS), and decreased the incidence of postoperative infectious complications. Mochiki et al<sup>9</sup> reported that glutamine could function as a motility-recovery agent after gastrectomy. However, Fujitani et al<sup>10</sup> reported that preoperative enteral immunonutrition did not show any clear advantage in terms of early clinical outcomes or modification of the systemic acute-phase response in gastric cancer patients. In recent years, three meta-analyses of enteral immunonutrition in patients undergoing gastric cancer surgery<sup>11-13</sup> and a review article of perioperative nutrition in patients with gastric cancer<sup>14</sup> were published. These articles, citing the above-mentioned Japanese articles, showed that perioperative, including preoperative, nutrition support with or without immune-stimulating nutrients is effective for enhancing patients' immunity and relieving the inflammatory response. However, there is no clear evidence of improving the clinical outcomes of patients with gastrectomy.

As the guidelines state, there is still insufficient evidence for this patient group, and further studies are needed.

## 2.3 | Access of gastrectomy

The original ERAS program included "short incisions." Under the ERAS approach, laparoscopic gastrectomy is prioritized. However,

oncologically, laparoscopic surgery is not permitted in all cases of gastric cancer.

Regarding early gastric cancer, a multicenter randomized controlled trial (RCT) describing the short-term outcomes of laparoscopic distal gastrectomy<sup>15</sup> and a meta-analysis concerning the long-term prognosis of laparoscopic distal gastrectomy<sup>16</sup> were published after the guidelines. At least in cases of distal gastrectomy for early stomach cancer, the outcomes of laparoscopic surgery appear comparable to those of open surgery. In Japan, a large-sized multicenter RCT (JCOG0912) is currently in progress; the results will be shown in recent years.<sup>17</sup>

The guidelines describe the technical aspects of laparoscopic total gastrectomy (LTG).<sup>6</sup> However, three meta-analyses compared the outcomes of laparoscopy with those of open total gastrectomy.<sup>18-20</sup> These papers described good outcomes of LTG despite some associated technical difficulties (Table 2).

Regarding the long-term prognosis of laparoscopic gastrectomy for advanced gastric cancer, we found one multicenter retrospective study,<sup>21</sup> three reviews,<sup>22-24</sup> and two meta-analyses (Table 3)<sup>25,26</sup> published after the guidelines. They showed that there were no marked differences in the long-term prognosis of laparoscopic and open gastrectomy. Large-scale, multicenter RCT investigating the long-term prognosis of laparoscopic gastrectomy for advanced gastric cancer are awaited.

#### 2.4 | Nasogastric/nasojejunal decompression

Regarding nasogastric/nasojejunal decompression, the guidelines strongly recommend that nasogastric/nasojejunal tubes not be used routinely in the setting of ERAS protocols in gastric surgery.<sup>6</sup> Nine RCT and only two meta-analyses were cited as the bases for this recommendation, although the evidence level was not so high.

Our search for papers on nasogastric/nasojejunal decompression for gastrectomy published in or after 2014 showed two RCT<sup>27,28</sup> and two meta-analyses.<sup>29,30</sup> These papers strongly supported the recommendation of the guidelines. The notion that nasogastric/nasojejunal decompression after gastric cancer surgery is unnecessary has been strengthened by these papers. Also, one of the two RCT was a report from Japan;<sup>28</sup> hence, it suggests that the early removal of the nasogastric tube is gradually accepted in Japan as well as in other countries.

### 2.5 | Perianastomotic drains

Regarding perianastomotic drains, the guidelines recommend avoiding the use of abdominal drains in order to reduce the risk of drain-related complications and shorten the hospital stay after gastrectomy.<sup>6</sup> However, this recommendation was based on only two meta-analyses, and both of them examined only about 400 cases of gastrectomy.

One of the two meta-analyses, from the Cochrane library, was updated in 2015.<sup>31</sup> Unfortunately, we found no other new RCT nor meta-analyses concerning abdominal drain placement after

Meta-analyses of laparoscopic vs open total gastrectomy, showing good short- and long-term outcomes of LTG TABLE 2

			Short-term outcome						Long-term outcom
Author	z		Operation time	Blood loss	Analgesics use	Hospital stay	Morbidity	Harvested lymph nodes	5-y OS
Shen et al <sup>18</sup>	1161	LATG 409	÷	$\rightarrow$	$\rightarrow$	$\rightarrow$	no change	no change	no change
		OTG 752							
Wang et al <sup>19</sup>	1498	LTG 559	~	$\rightarrow$	$\rightarrow$	$\rightarrow$	no change	no change	None
		OTG 939							
Wang et al <sup>20</sup>	2313	LTG 955	÷	$\rightarrow$	$\rightarrow$	$\rightarrow$	no change	no change	no change
		OTG 1358							

L(A)TG, laparoscopic (-assisted) total gastrectomy; OS, overall survival; OTG, open total gastrectomy.

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				DFS		OS			Cancer-related
Author	N		Cohort	3-у	5-у	3-у	5-у	Recurrence	death
Zou et al <sup>25</sup>	2596	LG 1328 OG 1268	Advanced	no change	no change	no change	no change	None	None
Chen et al <sup>26</sup>	7336	LG 3368 OG 3968	Early + advanced	None	None	None	no change	no change	no change

**TABLE 3** Meta-analyses of the long-term prognosis of laparoscopic gastrectomy for advanced gastric cancer

There was no marked difference in the long-term prognosis of laparoscopic and open gastrectomy.

DFS, disease-free survival; LG, laparoscopic gastrectomy; OG, open gastrectomy; OS, overall survival.

gastrectomy. Although we did find several retrospective analysis papers published after 2014, they all suggested that abdominal drain placement was unnecessary or only necessary in high-risk cases.<sup>32-34</sup>

As mentioned, we also could not find any RCT nor meta-analyses for abdominal drain placement from Japan. Does this indicate that it has already been generalized not to place an abdominal drain after gastrectomy in Japan? The answer is probably "No." There are many papers on "drain amylase" and we easily found three recent retrospective studies on the measurement of amylase level in drainage fluid from Japan.<sup>35–37</sup> As a result of the existence of these papers, it is presumed that an abdominal drain is placed after gastrectomy in many Japanese institutes. Although the authors argue that the measurement of amylase level in drainage fluid can predict early detection of pancreatic fistula, there is no evidence that it contributes to improve the patient's short-term prognosis.<sup>35–37</sup>

Japanese surgeons may seriously consider that pancreatic fistula leads to mortality after D2 surgery; however, pancreatic fistula is less observed after D0 or D1 surgery which had been standard surgery in Western countries. Although Western and some Asian studies suggest that abdominal drain placement after gastrectomy is basically unnecessary or even harmful, "no drainage tube" would not be accepted without more advanced evidence on the benefit and risk of "no drainage tube" after D2 surgery in Japan.

# 2.6 | Early postoperative diet and artificial nutrition

Regarding early postoperative diet and artificial nutrition, recommendations of the guidelines seem challenging. Although the guidelines did not clearly describe when to start oral intake with respect to type of gastrectomy, the guidelines supported early food ingestion after gastric cancer surgery based solely on the fact that no trial has reported any adverse events as a result of early food ingestion. For patients who received total gastrectomy, the guidelines recommend that drink and food should be offered at will from 1 day after surgery. For patients who are malnourished or have not reached 60% of desired intake until 1 week after surgery, the guidelines recommend individualized nutritional support.<sup>6</sup>

From outside Japan, we found one RCT and three retrospective studies concerning early diet after gastrectomy published in or after 2014,<sup>38-41</sup> and two of them focused on total gastrectomy.<sup>40,41</sup> All

four papers mentioned the feasibility and safety of early oral feeding after gastrectomy.

In contrast, to start early diet after gastric cancer surgery in Japan, it may be necessary to consider the differences of medical conditions and surgical procedures between Japan and other countries. As Hirao et al<sup>42</sup> reported that patient-controlled dietary schedule improved clinical outcome after gastrectomy in 2005, some gastric surgeons in Japan consider that there is difficulty in uniformly starting early postoperative diet after gastrectomy. Figure 2 shows the starting day of oral feeding after gastrectomy in some Japanese hospitals,<sup>43</sup> and from this figure, it is presumed that a uniform opinion of Japanese surgeons for the starting day of oral feeding after gastrectomy is not yet provided. In 2018, a multicenter RCT on the effects of early oral feeding on length of hospital stay following gastrectomy has been reported from Japan.<sup>44</sup> This report showed that early oral feeding did not shorten postoperative hospital stay and increased postoperative complications after distal gastrectomy, and may shorten postoperative hospital stay after total gastrectomy. In Japan, the merits and demerits of early postoperative diet after gastrectomy are still controversial.

# 3 | CURRENT STATUS AND FUTURE PROSPECTS OF ERAS FOR GASTRIC CANCER SURGERY

Regarding the current state of the ERAS protocol in the field of gastric cancer surgery, four meta-analyses have been published in or since 2017 (Table 4).<sup>45-48</sup> Li et al and Li et al focused on the outcomes of ERAS in patients undergoing laparoscopic gastrectomy. They also showed that ERAS contributed to shorter postoperative hospital stay, rapid postoperative recovery, and decreased cost without increasing complications or readmission rate among patients undergoing laparoscopic gastrectomy.<sup>46,47</sup> Ding et al and Wang et al focused on the outcomes of ERAS in patients undergoing gastrectomy.<sup>45,48</sup> Ding et al showed that ERAS contributed to improvement of postoperative inflammatory response but increased readmission rate, and there were no significant differences in intraoperative parameters and postoperative complications.<sup>45</sup> In contrast, Wang et al showed that ERAS resulted in accelerated convalescence, reduction of surgical stress and



**FIGURE 2** Start date of oral feeding in Japanese hospitals (modified and excerpted).<sup>43</sup> POD, postoperative day; TG, total gastrectomy; DG, distal gastrectomy



Author	Cohort	Postoperative hospital stay	Postoperative complication	Postoperative recovery	Cost	Readmission rate	Other
Ding et al <sup>45</sup>	Gastrectomy	$\downarrow$	$\rightarrow$	n.a.	$\downarrow$	↑	
Li et al <sup>46</sup>	LAG	$\downarrow$	$\rightarrow$	↑	$\downarrow$	$\rightarrow$	
Li et al <sup>47</sup>	LAG	$\downarrow$	n.a.	n.a.	$\downarrow$	n.a.	
Wang et al <sup>48</sup>	Gastrectomy	n.a.	n.a.	↑	$\downarrow$	n.a.	Improve nutrition status, better QOL

All papers showed that the ERAS protocol reduced the cost and duration of hospital stay without increasing surgical complication rates, suggesting that ERAS is effective in gastric cancer surgery.

LAG, laparoscopy-assisted gastrectomy; n.a., not available; POD, postoperative day; QOL, quality of life.

medical costs, improved nutritional status, and better quality of life for gastric cancer patients.<sup>48</sup>

Almost all of these papers showed that the ERAS protocol helped reduce cost and shorten hospital stay without increasing surgical complication rates, suggesting that ERAS is effective in gastric cancer surgery (Table 4).

These findings show that the usefulness of the ERAS protocol for gastrectomy is receiving widespread recognition in countries outside of Japan. However, regarding its recognition inside Japan, Gastric Cancer Treatment Guidelines 2018 showed a model case of the clinical pathway after gastrectomy in the section "Clinical pathway after gastric cancer surgery" (Table 5).<sup>49</sup> Using this approach, the nasogastric tube is recommended to be removed by postoperative day (POD) 1, drinks are recommended to be offered after POD 1, food recommended to be offered from POD 2-4, and the drain (if placed) is recommended to be removed by POD 5. Although this may be the average postoperative course in Japan, it seems a bit slow from the viewpoint of ERAS.

In the previous section, we introduced papers from Japan on each element, but, compared with reports from other countries, we have the impression that there are few reports of RCT or metaanalysis from Japan. Therefore, from this point of view, perioperative care by ERAS seems not to have been generalized in Japan.

**TABLE 5**Model case describing the clinical pathway aftergastrectomy (partially modified and excerpted)

Clinical element	Recommendation
Removal of nasogastric tube	By POD1
Start drinking	After POD1
Start eating solid food	From POD2-4
Removal of abdominal drain	By POD5

Using this approach, the nasogastric tube is recommended to be removed by postoperative day (POD) 1, drinks are recommended to be offered after POD 1, food recommended to be offered from POD 2-4, and the drain (if placed) is recommended to be removed by POD 5.

Why is ERAS not readily acceptable in Japanese gastric cancer society? As mentioned at the beginning, the aim of ERAS is to reduce surgical complications or surgical stress, strengthen resilience, shorten hospital stay, improve safety, and reduce costs. However, previous reports lack the view point of patient's anxiety or satisfaction when applying ERAS. These psychological factors are related not only with perioperative care but with medical costs and the social insurance system. Some say that the difference in the social system (especially the insurance system) or the difference in medical conditions or surgical procedures for gastric cancer makes it difficult to apply the original ERAS policy. Thus, what kind of effort should we make to spread ERAS? First, we must collect data on retrospective analyses in Japanese gastric cancer surgical patients and understand the current status of Japanese gastric cancer treatment. Then, we must make an effort to devise a new ERAS protocol appropriate to Japanese conditions of gastric cancer, or to seek an appropriate cohort to apply the ERAS protocol. As an example of such efforts, we introduce the ESSENSE (essential strategy for early normalization after surgery with patient's excellent satisfaction) project by the Japanese Society for Surgical Metabolism and Nutrition.<sup>50</sup>

## 4 | CONCLUSION

We introduced consensus guidelines for enhanced recovery after gastrectomy and explained the usefulness of the ERAS protocol in the field of gastric cancer surgery. However, most evidence is established in Western countries where gastric cancer surgery is different from Japan. Although introducing the concept of ERAS into gastric cancer surgery may help to improve the perioperative environment of patients, there is little evidence reported from Japan. Future study must focus on developing a new ERAS protocol appropriate to Japanese conditions of gastric cancer.

#### DISCLOSURE

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#### ORCID

Takaki Yoshikawa ២ https://orcid.org/0000-0003-1936-9484

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