



A clinical study on gastric cancer patients administered EN and PN versus PN alone in enhanced recovery after surgery

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Background and objectives: Enhanced recovery after surgery (ERAS) recommends avoiding enteral nutrition (EN) due to undesirable sequelae such as pulmonary aspiration and infections. Not using of EN in nongastric resections under ERAS pathways is often successful. However, parenteral nutrition (PN) alone followed by early postoperative oral feeding in gastric cancer patients, recommended by the ERAS guidelines, has unclear benefit and is only adopted after gastric resection. This study aimed to compute the postoperative outcomes of EN and PN compared to those of the ERAS-recommended nutritional pathway. Our secondary objective was to compare postoperative complications between the two groups.

Materials and methods: Of 173 gastrectomy patients, 116 patients were in the combined group (EN and PN), whereas 57 patients were in the PN alone group. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 26.0.0 software. The data were analyzed by one-way ANOVA, the independent sample *t*-test, or, in the case of several independent samples, by the Kruskal–Wallis test. Categorical data were analyzed by Pearson's χ^2 test or Fisher's exact test.

Results: The observed indices included C-reactive protein (CRP), platelet (PLT), white blood cells (WBC), hemoglobin (Hb), albumin, and PRE-albumin. The secondary outcomes included length of hospital stay (LOS), cost, incidence of pulmonary infection, and total incidence of infection.

Conclusion: The combined mode of nutrition is feasible and is not associated with postoperative complications in gastric cancer patients under ERAS.

Keywords: EN feeding tubes, ERAS, gastric cancer, PN

Introduction

Adenocarcinoma is the most common type of gastric cancer, accounting for up to 90% of all stomach cancers^[1]. Surgery is the only curative pathway for treating gastric cancer, but its insult usually results in catabolism due to surgical stress^[2,3]. However, compared with previous surgical standards, the advent of enhanced recovery after surgery (ERAS) conveys a favorable prognosis^[4–7]. Comparative studies between ERAS and conventional methods have shown that ERAS is superior to conventional methods. Hence, ERAS protocols are recommended in several surgical departments^[8–10]. Despite extensive acclaim, some of its pathways are difficult to comply with.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2024) 86:1433–1440

Received 25 October 2023; Accepted 28 December 2023

Published online 24 January 2024

<http://dx.doi.org/10.1097/MS9.0000000000001753>

HIGHLIGHTS

Enhanced recovery after surgery (ERAS) recommends the elimination of enteral nutrition (EN) due to undesirable sequelae such as pulmonary aspiration and infections. Benign neglect of EN in nongastric resections under ERAS pathways is often successful. However, parenteral nutrition (PN) alone followed by early postoperative oral feeding in gastric cancer patients recommended by ERAS guidelines is indistinct and merely adopted in gastric resections. This study's objective was to compute the postoperative outcomes of EN and PN compared to the ERAS-recommended nutritional pathway. Our secondary objective was to observe postoperative complications between the two groups.

- This study recommends a combination of EN and PN immediately after gastric resections in ERAS pathways.
- Combined nutrition (EN and PN) is necessary, innocuous, feasible, and more beneficial in gastric cancer resections under the ERAS guidelines. We propose that EN elimination lacks significant evidence in gastric resections.
- EN and PN does not increase the incidence of postoperative complications in patients and is beneficial for postoperative recovery

Enteral nutrition (EN) and parenteral nutrition (PN) are expected to serve the same purpose, but they have differences. EN is believed to preserve the mucosal structure, microbiota, and

gut-associated lymphoid tissue; stimulate early gut function; and improve both hepatic and pulmonary functions^[11,12]. PN is chiefly recommended when the gastrointestinal tract is dormant or when it is urgent to restore nutritional status^[13,14].

It is necessary to integrate EN and PN in gastric resections within the ERAS pathway, as they significantly impact patient outcomes and play a crucial role in recovery. The difference between EN and PN under ERAS pathways is not often evaluated since eliminating EN after surgery is recommended.

The current ERAS guidelines suggest that patients be given oral fluids immediately after surgery to avoid EN. Mortensen *et al.*^[15] concluded that a nasogastric tube should not be placed in patients with gastric cancer. Unfortunately, the amount of food consumed orally consumed shortly after gastric surgery is minimal. Therefore, an alternative approach to eliminating nutritional risks and improving patient outcomes in patients with gastric malignancies, beyond the ERAS guidelines, is imperative. PN alone is the most common routine under ERAS guidelines.

EN has advantages over PN^[16], but EN might be associated with a burden of tube-related pulmonary infections, which could provoke an immune response, delay recovery, prolong hospital stays, and raise costs. Furthermore, it is well understood that PN is recommended mainly for patients with severe or prolonged ileus^[17,18]. Due to its fewer postoperative complications, ERAS can reduce patient hospitalization costs^[19,20]. Another study on ERAS in colorectal cancer patients suggested that ERAS can increase cost-effectiveness and improve the quality of medical care^[21].

There are unanswered questions about feeding tubes under ERAS pathways. First, is it necessary to insert EN combined with PN under ERAS guidelines? Second, is EN feasible in the ERAS setting? Third, are complications associated with EN combined with PN inevitable? We designed this research to analyze post-operative manifestations in patients administered either EN and PN combined or PN alone after surgery under the ERAS guidelines to determine whether combined EN and PN is necessary,

feasible and safe. In this study, we analyzed two groups of patients treated with different nutritional administration methods under the ERAS guidelines. In the combined group, patients were administered EN via the nasojejunal route and/or PN via the intravenous route. None of the patients in this retrospective study underwent percutaneous endoscopic gastrostomy, because patients given percutaneous endoscopic gastrostomy often have chronic underlying disease or vulnerable general conditions or are unable to receive EN through nasogastric or nasojejunal feeding tubes^[22].

Materials and methods

Medical records of patients who underwent resection for gastric malignancies between February 2020 and November 2021 were searched. Two groups of surgeons who randomly performed the surgeries could be distinguished in the patients' medical records: one group used both EN and PN combined, while the other group eliminated EN. Perioperative patient data, including nutritional mode, could also be retrieved from their respective medical records. A total of 740 gastrointestinal resection case reports were detected, and only 173 patients met the inclusion criteria (Image 1). A total of 116 patients were included in the combined group, whereas 57 patients were included in the PN group (Image 1). All these patients had histologically confirmed gastric malignancies.

Inclusion and exclusion criteria

Inclusion criteria: (1) aged 18–80 years; (2) did not receive chemotherapy or other antitumor treatments before surgery; (3) underwent elective D2 surgery; (4) underwent ERAS; (5) received nasojejunal tubes such as EN combined with PN, indicated as the nutrition tube group (NTG), or did not use EN or the nonenteral nutrition tube (NeTG) (Table 1); and (6) provided informed consent from the patients and their families.

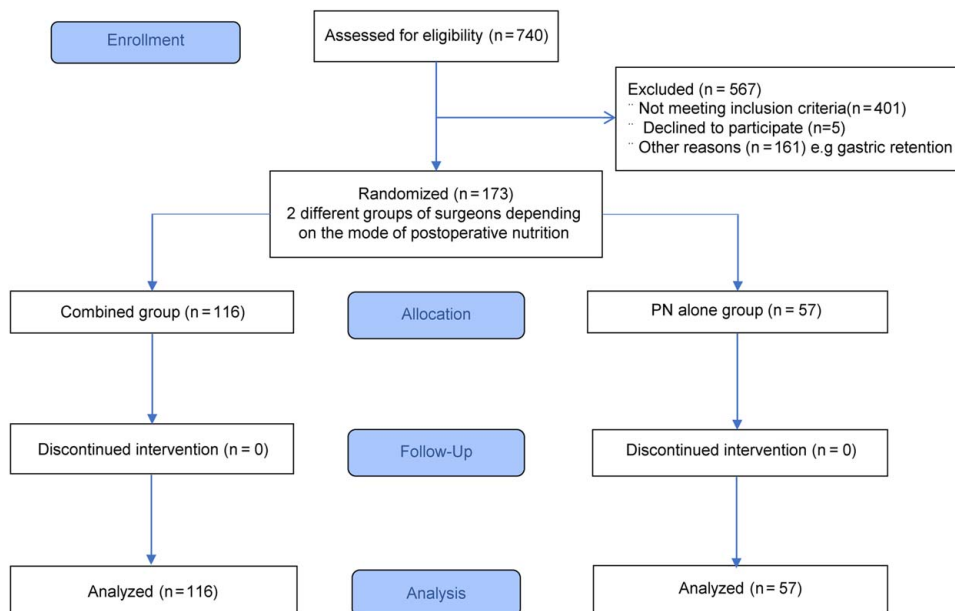


Image 1. Consolidated standards of reporting trials flow diagram.

Table 1
ERAS protocols employed in the study hospital

	Preoperative		Operative		Postoperative	
			After surgery	POD 1	POD 2-4	POD 5
Multidepartment team screening (MDT)	Screening		Surgical approach	Screening	Follow-up	Screening
Carbohydrates	600 ml 2–4 h prior to surgery					
Fluid			Balanced iv fluid		(NeTG) 2000–3000 ml PN	
Nutrition	Regular diet		Clear fluids 2 h before anesthesia	(NTG) EN was administered depending on patients weight	(NTG) Combined EN and PN: Enteral Nutritional Suspension (SP)	Commencement of oral fluid diet until discharge
Evaluation of gastric retention	Yes			(NeTG) PN alone	Evaluated in both groups	
Prophylaxis	Antibiotic prophylaxis 1 g cefmetazole sodium iv (MDT)	If the operation is over 2 h, 1 g cefmetazole sodium iv		1 g cefmetazole sodium iv for the first 3 days		
Temperature	(MDT)		Intraoperative temperature monitoring		After every 4 h until discharge	
Bowel preparation	No					
Surgical approach	(MDT)	Minimal invasive is preferred unless otherwise				
Feeding tubes			Randomly selected	(NTG) or (NeTG)		Remove
Drainage tube			Yes	»	»	Remove
Urinary catheter			Yes	»	Remove	
Analgesia	NSAIDs (IM)		Low opiate dose and TAP	lv NSAIDs every 12 h for the first 3 days		
Ambulation			Bed activities	Bedside walking	Walking in hospital corridor	Normal ambulation

Exclusion criteria: (1) gastric cancer causes complications (bleeding, obstruction, or perforation) and obstructive symptoms; (2) major cardiovascular disease, respiratory, and renal dysfunction, history of myocardial infarction or cerebrovascular accident within the past 6 months, and history of upper abdominal surgery; (3) gastric cancer recurrence, distant metastasis, combined organ resection; (4) severe obesity (BMI > 30 kg/m²) or severe malnutrition (BMI <15 kg/m²).

Data recording and collection

The EN tube was placed mechanically at the end of each surgery by specialists. Imaging studies confirmed the correct positioning of the lesion at a level beyond the anastomotic plane, aiming to minimize the incidence of infections and anastomotic leakage. Immune and inflammatory indices were collected before surgery, followed by morning blood sample collection during the entire inpatient period. All the clinical indices presented in this article were laboratory analyzed from blood samples.

The accumulated data from the patients’ medical records were searched manually for significant variables, including patient age, sex, weight, BMI, inflammatory markers, immune cells, length of hospital stay (LOS), pulmonary infections, total incidence of complications, and cost.

A thin nasojejunal polyurethane feeding tube (size 10F, Flocare, Beijing L&Z Medical Technology Development Co., Ltd.) was placed on the well-ventilated side of the nasal cavity in all NTG groups immediately after surgery. The tube was flushed every 8 h with 25–50 ml of warm water to avoid pipeline blockage.

The EN contents included water, maltodextrin, whey protein hydrolysate, vegetable oil, vitamins, minerals, microelements, and other essential nutrients. Each patient was administered

~2000 kcal/day, which is equivalent to four bottles (500 ml/bottle/day), though this amount varied according to the patient’s weight. The initial starting dosage was 1000 kcal/day, equivalent to two bottles with 500 ml/bottle. Treatment was stopped if the patient had gastrointestinal failure, complete intestinal obstruction, or severe intraperitoneal infection.

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 26.0.0 software (SPSS, Inc.). The normality of data distributions were tested with the Kolmogorov–Smirnov test. Normally distributed data were analyzed by one-way ANOVA or the independent sample *t*-test and are presented as the mean ± SD. Nonparametric data were analyzed by the Mann–Whitney *U* test (two independent samples) or the Kruskal–Wallis test (≥ 3 independent samples). Categorical data were analyzed by Pearson’s χ^2 test or Fisher’s exact test.

Results

Among the 173 patients in the combined group, 116 met the inclusion criteria, whereas 57 patients in the PN alone group met the inclusion criteria. The patients’ preoperative parameters are indicated in Table 2. Of the 116 patients in the combined group, 40 were female and 76 were male, whereas 57 patients in the PN alone group consisted of 25 females and 32 males. The preoperative and postoperative parameters that were observed included C-reactive protein (CRP), white blood cell (WBC) count, platelet (PLT) count, hemoglobin (Hb), albumin, pre-albumin, hospital cost, LOS, total incidence of complications, and

Table 2
Demographic parameters of patients included in the study

Characteristics	Mode of nutrition	N	Mean \pm SD	P-value of significance
Age (years)	Combined	116	66.67 \pm 8.22	0.271
	PN	57	65.12 \pm 9.53	
Sex (F/M) n	Combined	116	40/76	0.246
	PN	57	25/32	
Weight (kg)	Combined	114	63.13 \pm 10.40	0.118
	PN	57	66.07 \pm 13.56	
BMI (kg/m ²)	Combined	114	23.58 \pm 2.98	0.275
	PN	57	24.15 \pm 3.56	
CRP (mg/l)	Combined	89	2.69 \pm 5.75	0.480
	PN	35	3.87 \pm 12.67	
WBC (X 10 ⁹)	Combined	110	6.26 \pm 1.88	0.520
	PN	53	6.60 \pm 4.75	
Hb (g/l)	Combined	110	119.70 \pm 23.98	0.006
	PN	53	130.60 \pm 22.16	
PLT (X 10 ⁹)	Combined	111	233.90 \pm 89.26	0.019
	PN	52	200.60 \pm 71.06	
Albumin (g/l)	Combined	110	38.06 \pm 3.63	0.578
	PN	53	38.47 \pm 5.70	
Pre-Albumin (mg/l)	Combined	15	183.30 \pm 57.50	0.901
	PN	10	186.40 \pm 65.84	

pulmonary infection. For the preoperative parameters, no significant differences were observed between the two groups in patient age, sex, weight, BMI, CRP, or pre-albumin. There was a significant difference in Hb and PLT between the two groups (Table 2).

Clinical indices

WBC

Compared with that in the PN alone group, the WBC count was lower on the third postoperative day in the combined group ($P < 0.05$). These results indicate that the patients in the combined group had improved inflammation and infection levels (Table 3).

CRP

Compared with that in the PN alone group, the CRP level was lower on the first and third postoperative days in the combined

group ($P < 0.05$). This specific marker was used to equate the levels of inflammation after surgery. These results indicate that patients in the combined group had improved inflammation and infection levels (Table 3).

PLT

A significant difference between the two study groups was observed. Patients in the combined group had more PLTs than those in the PN alone group on the first and third postoperative days ($P < 0.05$) (Table 3).

Hb

When we compared the Hb levels of the two groups at the first, third, fifth, and seventh postoperative days, there was no significant difference (Table 3).

Albumin

While a significant difference was obvious between the groups on the third, fifth, and seventh postoperative days ($P < 0.05$), the albumin levels increased in both groups. Due to the nature of gastric cancer resection, most patients have higher inflammatory levels associated with disease and nutritional risks even before surgery. However, these levels were remedied after tumor resection and the commencement of feeding tubes. On postoperative Day 1, the PN alone group had similar albumin levels to those of the EN + PN group (Table 4).

Pre-albumin

On the third, fifth, and seventh postoperative days, pre-albumin in the pEN + PN group was significantly higher than that in the PN group. This finding is consistent with the change trend of albumin (Table 4).

The secondary outcomes included postoperative pulmonary infections, LOS, and total incidence of infections.

Cost

The postoperative hospital cost was calculated, excluding the preoperative or operative cost. The currency used was the Chinese yuan, which had an estimated rate of 1 USD = 6.5

Table 3
Comparison of CRP levels, WBC counts, PLTs, and HBs

Day	CRP		WBC		PLT		HB		
	Mean \pm SD	P	Mean \pm SD	P	Mean \pm SD	P	Mean \pm SD	P	
1	Combined	50.17 \pm 29.39	0.0415	14.64 \pm 11.79	0.1591	216.30 \pm 79.90	0.0212	116.60 \pm 19.09	0.0666
	PN	61.39 \pm 40.39		12.38 \pm 3.30		189.40 \pm 49.52		122.10 \pm 15.86	
3	Combined	54.63 \pm 40.35	0.0416	8.57 \pm 2.61	0.0349	210.90 \pm 75.79	0.0446	112.10 \pm 19.07	0.0579
	PN	70.66 \pm 49.85		9.56 \pm 3.05		187.90 \pm 46.52		118.20 \pm 18.05	
5	Combined	29.89 \pm 34.36	0.7315	6.89 \pm 2.42	0.9688	231.30 \pm 91.75	0.0686	112.10 \pm 15.43	0.0758
	PN	31.98 \pm 26.11		6.92 \pm 4.86		204.20 \pm 67.30		117.20 \pm 14.72	
7	Combined	15.59 \pm 20.35	0.4748	6.95 \pm 2.76	0.3389	249.60 \pm 99.68	0.1549	112.30 \pm 15.25	0.1511
	PN	18.63 \pm 19.94		6.48 \pm 2.09		225.50 \pm 60.59		116.70 \pm 14.41	

Creatinine reactive protein (CRP); hemoglobin (Hb); platelets (PLTs); white blood cells (WBCs).

Table 4
Comparison of nutritional parameters

Day		Albumin g/l		PRE-Albumin mg/l	
		Mean ± SD	P	Mean ± SD	P
1	Combined	34.16 ± 3.64	0.1024	192.00 ± 46.91	0.8096
	PN	33.20 ± 2.70		189.90 ± 50.12	
3	Combined	34.46 ± 3.67	0.0321	159.00 ± 44.67	0.0437
	PN	33.12 ± .54		140.5 ± 36.55	
5	Combined	34.27 ± 3.21	0.0251	172.20 ± 42.34	0.0405
	PN	32.98 ± 3.01		151.20 ± 47.34	
7	Combined	34.99 ± 3.41	0.0270	176.10 ± 58.69	0.0273
	PN	33.42 ± 3.87		138.00 ± 242.56	

Chinese yuan. The patients in the combined group spent less during the postoperative period than the PN alone group (mean ± SD = 6000.46 ± 1338.88 and 7958.21 ± 1762.77) ($P < 0.05$) (Table 5).

Postoperative cost and LOS

The patients in the combined group spent fewer postoperative days than those in the PN alone group (mean ± SD = 13.56 ± 4.99 and 17.04 ± 11.45, respectively), and the pooled result was significant (P -value = 0.029) (Table 5). A shorter duration of hospital stay was a result of limited postoperative complications. Generally, the expenditures of the patients in the combined group were far less than those in the PN alone group. This strategic approach of implementing combined feeding tubes in ERAS pathways has led to the use of buoyed EN, as it is both more beneficial and less expensive. Evidently, this low-cost method was also associated with fewer complications, a reduction in medications and early discharge. This cost-efficient model is crucial to patient prognosis, financial capabilities, and patient satisfaction and plays a vital role in managing hospital resources (Table 5).

Postoperative complications

The probability of any postoperative complication in the combined group was significantly lower than that in the control group, though there was no significant difference in the incidence of pulmonary infection between the two groups. This finding indicates that placing a feeding tube during the operation does not increase the probability of pulmonary infection after the operation (Fig. 1). The Clavien–Dindo complication grades are given in Table 6.

Table 5
Postoperative cost and hospital stay

	N	Mean ± SD	P-value of significance
Postoperative cost			
Combined	116	6000.46 ± 1338.88	0.00
PN	57	7958.21 ± 1762.77	
Postoperative LOS			
Combined	116	13.56 ± 4.99	0.029
PN	57	17.04 ± 11.45	

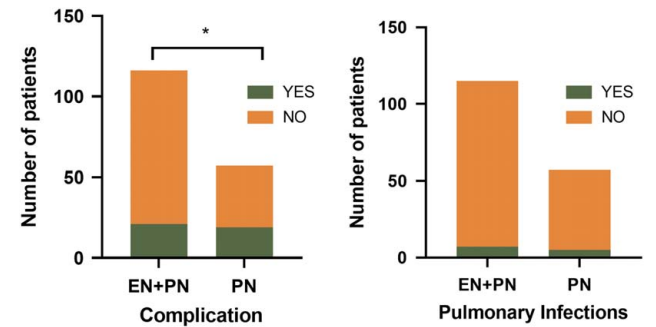


Figure 1. Comparison of the total incidence of complications and of pulmonary infection between the combined group and parenteral nutrition group.

Discussion

Albumin and pre-albumin levels are only used to assess inflammation in the context of malnutrition risk and not explicitly to determine the malnutrition risk. It was previously suggested that the serum albumin level is associated with the acute-phase response to tissue catabolism and inflammation. Another study confirmed the significance of the serum ALB concentration for inflammation and postoperative prognosis. The authors also demonstrated the importance of EN after surgery^[23,24].

In our study, the albumin in the PN group was not significantly different 1 day after surgery from that in the combined group. However, a few days after surgery, the patients in the combined group had improved levels of albumin and pre-albumin compared to those in the PN alone group.

ERAS recommends EN omission due to the presupposed distress of irritation, incidence of pulmonary aspiration, infections, and tube malpositioning^[25]. These dogmas have influenced ERAS studies, leading them to advocate eliminating the use of EN in theory. For this reason, some ERAS studies reject the use of EN or EN combined with PN. Remarkably, our study showed no significant difference between the two groups in terms of EN-related side effects, such as pulmonary infections. This could be caused by the mechanical placement of the EN tube during the intraoperative period and observation of the tube guided by imaging studies.

It is unquestionable that decreased infection rates, nutritional risk, inflammation, and complications followed by enhanced immunity and tissue healing increase patient mobility and reduce the LOS and cost^[7,26–28]. This typical benefit was also observed in our study and other previously recorded data from non-ERAS studies^[29–33].

To address potential biases of our study, surgeries selected for retrospective analysis were randomly chosen from among those performed by two experienced surgeons (NTG and NeTG),

Table 6
Clavien–Dindo classification of postoperative complications

Determinant	Combined	PN	χ ² -value	P
Grade I	9	11		0.670
Grade II	7	6		
Grade III	2	2		
Grade IV	2	0		

where the severity of malignancy, age, sex, or metastasis did not play any role in grouping the patients between the two surgical units. Other related biases could be linked to disease progression in different individuals and to the study duration.

Studies have reported incidences of postoperative nasogastric tube-associated complications resulting from patient discomfort, anxiety, depression, and delirium^[30,34,35]. Moreover, EN alone has been reported to increase postoperative immune T-cell levels and improve patients' nutritional status and energy levels at a lower cost. Furthermore, a meta-analysis showed no significant difference between EN alone and PN alone in terms of postoperative EN-related pulmonary infections^[36,37]. Dorota *et al.* reported the beneficial effect of combined nutritional treatment on significant improvements in inflammatory biomarkers, such as albumin and pre-albumin. Two separate meta-analyses concluded that combining EN and PN increased the albumin and pre-albumin levels^[38,39]. Several studies have shown that EN combined with PN is feasible and safe and improves immunological function compared to EN or PN alone^[40,41]. Even though several studies favor EN or EN combined with PN, stringent ERAS evaluation of gastric malignancies is challenging, as ERAS studies limit EN administration, making our rationale exceptional within the ERAS literature.

Total oral intake is mostly feasible 1–2 weeks after surgery. The surgical patient already has a cancerous physique and only depends on a small amount of clear fluid during the early postoperative days; this amount is nutritionally insufficient and further diminishes patients' nutritional values and immune responses, stimulating inflammation, and delaying recovery. A prior ERAS study revealed that the recommended early postoperative intake of clear fluid alone might not improve patient outcomes^[36]. We can argue that gastric cancer patients undergoing ERAS protocols might be at risk of malnutrition after gastric cancer resection. Therefore, EN elimination should not be routinely recommended in gastric resections^[3]. Notably, benign omission of EN after nongastrointestinal resection under ERAS guidelines is often successful. However, the use of early postoperative oral feeding and the exclusion of feeding tubes in gastric cancer patients has uncertain benefits and has rarely been tried.

This study recommends a combination of EN and PN immediately after gastric resection via the ERAS pathway. Our results can be summarized as follows: when EN and PN are combined, there are fewer anorexigenic features, an enhanced response to surgery and immunity, fewer postoperative complications, and greater recovery after surgery, as well as a shorter LOS and lower cost compared to EN omission as proposed by the current ERAS guidelines. These findings demonstrated that the patients in the combined group improved in both pathological and physiological responses to surgery, as the levels of surgical stress-related inflammation and infections decreased in the combined group compared to the PN alone group.

Conclusion

Combined nutrition (EN and PN) is necessary, innocuous, feasible and more beneficial in gastric cancer resections under the ERAS guidelines. We propose that EN omission is not backed by strong evidence after gastric resection. Furthermore, mechanical placement of the EN tube supported by imaging studies can limit complications of EN. ERAS policy-makers should further

evaluate the necessity of EN in select patients who have undergone gastric cancer resection, as the need to maintain and improve patient physiology outweighs the burden accompanying its use.

Study limitations

This study included a few ERAS patient samples, as patients who could tolerate early oral feeding did not need any form of tube feeding. Some patients had EN interruption due to GI dysfunctions. Preoperative parameters were compared between the PN + EN group and the PN group, and differences in Hb and PLT were detected, which affected the comparability of the comparison groups and may have resulted in confounding bias. Moreover, we did not consider the magnitude of the effect sizes when explaining the results, which could affect the credibility of the results. The study was also limited to a single center, the sample was small, and the number of patients analyzed for each variable was not consistent. All the qualitative studies that used EN were not performed under ERAS protocols.

Ethical approval

Ethical approval for this study (Ethical number: 2016035) was provided by the Ethics Committee of Jiangbin Hospital on 02 March 2016. The address of the ethics committee: 438 Jiefang Road, Jingkou District, Zhenjiang City, Jiangsu Province, China. All procedures used in this study complied with the WMA Declaration of Helsinki ethical principles for medical research involving human subjects. All patients under ERAS protocols in Jiangbin Hospital were adequately informed about their involvement in this research program and willingly gave their consent. This study has been registered at the Chinese Clinical Trials Registry (ChiCTR2300068532).

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Sources of funding

Jiangsu Commission of Health (Grant numbers: LKZ2023012). Social Development Project of Zhenjiang City (Grant numbers: SH2022061).

Author contribution

J.C.: study design; X.F.: writing the paper; Y.X., R.W., L.Z., and H.H.: research design, implementation of specific measures, and data collection; H.H.: data analysis and interpretation.

Conflicts of interests disclosure

The authors declare no conflicts of interests for this article.

Research registration unique identifying number (UIN)

ChiCTR2300068532. <https://www.chictr.org.cn/showproj.html?proj=180393>

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Animal studies

None.

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