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Effect of sequential *vs.* non-sequential early enteral nutrition therapy on nutritional status, recovery, and quality of life of patients with esophageal cancer

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Abstract. – OBJECTIVE: To study the effects of early sequential enteral nutrition (ESEN) therapy and early non-sequential enteral nutrition (EN) therapy on the nutritional status, recovery, and quality of life of patients who undergo postoperative chemotherapy for esophageal cancer.

PATIENTS AND METHODS: The data of 90 patients who underwent postoperative chemotherapy for esophageal cancer in Gansu Provincial Cancer Hospital from January 2018 to June 2020 were analyzed retrospectively. Patients were divided the Test group and the Control group (n=45 each) based on the method of nutritional support. Patients in the Control group were treated with non-sequential early enteral nutrition and the Test group treated with sequential early enteral nutrition until the discharge. Nutritional status, recovery, and quality of life of the chemotherapy patients in the two groups were compared.

RESULTS: After the intervention, the pre-protein, albumin and hemoglobin levels were higher in the Test group than in the control group ($p<0.05$). Postoperative exhaustion, incision healing and length of hospital stay were significantly lower in the Test group than in the Control group ($p<0.05$), while the scores on all dimensions of the short-form 36 health survey scale (SF-36) and the total score were higher than in the Control group ($p<0.05$).

CONCLUSIONS: Sequential early enteral nutrition may be used for patients who undergo chemotherapy after esophageal cancer surgery to promote their early recovery and improve their quality of life and nutritional status.

Key Words:
Sequential early enteral nutrition, Esophageal cancer, Nutrition, Postoperative recovery, Quality of life.

Introduction

Esophageal cancer is a common malignancy of the digestive system, with a high clinical incidence and a high mortality rate in China and worldwide, and surgery is considered a preferred method of treatment[1,2]. Esophageal cancer is associated with decreased immunity and physiological functions of the patients[3]. Traditional perioperative care focuses on the disease itself and emphasizes surgical intervention and symptomatic care. It also includes prolonged preoperative fasting and excessive postoperative rehydration that often cause water-electrolyte disbalance and malnutrition, which are extremely detrimental to postoperative recovery. Therefore, early and reasonable nutritional support is crucial to speed up the recovery process of post-operative esophageal cancer patients[3-5]. Studies[6-8] have shown that enteral nutrition (EN) support helps to maintain postoperative negative nitrogen balance in surgical patients and effectively improves malnutrition caused by stress hypermetabolism after the operation. EN can shorten the recovery process of intestinal peristalsis and gastrointestinal barrier function after surgical anesthesia. It can maintain moderate immune response and homeostasis of the internal environment by regulating the release of cytokines, reducing postoperative infection and other complications, thus shortening the postoperative recovery process. EN is highly beneficial in improving an overall patient's perioperative experience and quality of life[6-11]. Early sequential enteral nutrition (ESEN) gradually transits patients from amino acid and short peptide formula to whole protein formula according to the postoperative gastrointestinal reaction and vital signs of patients, which may be beneficial for improving the prognosis of esophageal cancer patients[12,13]. However, there is little literature on ESEN in patients with esophageal cancer after surgery. In the current retrospective study, we explore the

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effects of ESEN therapy and conventional EN therapy on the nutritional status and quality of life of patients with esophageal cancer after the surgery. The results of this study may provide a reference for the improvement of the quality of life of postoperative esophageal cancer patients.

Patients and Methods

Inclusion Criteria and Exclusion Criteria

Inclusion criteria

1. Patients diagnosed with esophageal cancer according to the accepted criteria[14] who are undergoing radical esophageal cancer surgery;
2. Patients with stage I and II lymph node metastasis according to the Tumor Node Metastasis (TNM) staging criteria established by the International Union Against Cancer[15];
3. Squamous carcinoma on histopathological examination;
4. Patients informed and agreed to the study;
5. Complete clinical records;
6. Patients are conscious and able to communicate.

Exclusion criteria

1. Distant metastases;
2. Metabolic syndrome;
3. Other organ lesions;
4. Immune dysfunction.

Clinical Data

The records of 90 patients who underwent chemotherapy after radical esophageal cancer surgery in Gansu Provincial Cancer Hospital from January 2018 to June 2020 were reviewed retrospectively. The Ethics Committee of Gansu Provincial Cancer Hospital approved this study on April 30th, 2020, with the No. P202004150014. The patients were divided into a sequential early enteral nutrition group (Test group, n=45) and a non-sequential early enteral nutrition group (Control group, n=45) according to whether they were sequentially transitioned from amino acid enteral nutrition to whole protein enteral nutrition after the operation. During the study period, both groups had no discontinuation or loss of follow-up.

The Test group comprised 26 males and 19 females; Aged 42-72 years, mean (59.60 ± 7.44) years; The weight of patients in the Test group was 42-84 kg, mean (65.93 ± 9.07) kg; 28 were at TNM stage I, 17 patients were in the stage II; 8 patients had a family history; 18 patients had a smoking history. In the Control group, there were 20 males and 25 females. Age ranged from 44 to 74 years, mean (61.07 ± 6.92) years. Weight ranged from 41 to 83 kg, mean (64.13 ± 9.13) kg; 23 were at TNM stage I and 22 were in stage II; Five patients had a family history, and 24 had a smoking history. The diversity in the general information between the two groups was not statistically significant (p>0.05) (Table I).

Methods

Both groups received early EN therapy and routine symptomatic support after the operation. Patients' total daily energy demand was calculated as 30 kcal/kg per day, and the total daily protein demand was calculated as 2 g/kg. After the conversion, 0.5 L of nutrients was pumped through the nasal duodenal catheter one day after the operation, and 1 L was pumped the next day. On the third day after the operation, after reaching half of the EN dose, patients in the two groups were allowed to drink a small amount of water or liquid food, and after completing the full dose of EN, a small amount of semi-liquid was ingested. On the 4th to 7th day after surgery, the daily intake of EN and oral intake of energy were 3:1, 1:1, 1:3, and 1:3, respectively. On the 7th day after the operation, if there was no fistula formation, the diet was changed to a full liquid/semi-liquid diet.

Patients in the Control group received an enteral nutrition reagent (LESKON, Xi'an, China), non-sequential EN formula that contained whole

Table I. Comparison of basic information between the two groups of patients.

General information	Test group (n=45)	Control group (n=45)	χ^2/t	p
Gender (Male/Female)	26/19	20/25	1.601	0.206
Age (Year)	59.60±7.44	61.07 ± 6.92	-0.968	0.336
Weight (kg)	65.93 ± 9.07	64.13 ± 9.13	0.938	0.351
TNM stage (I/II)	28/17	23/22	1.131	0.288
Family history (Yes)	8 (17.8)	5 (11.1)	0.809	0.368
Smoking history (Yes)	18 (40.0)	24(53.3)	1.607	0.205

protein based EN nutrients. The daily postoperative pumping rate was set at 20-25 ml/h on the first day, then 40-50 ml/h on the second day if the patient tolerated it well and had no significant nausea or vomiting, and then increased by 20-25 ml/h until 100 ml/h if patient tolerated it well.

Patients in the Test group started to receive the Amino acid EN nutrient (Vivonex, Basel, Switzerland) 1 day after the operation. If there was no abdominal distension and nausea on the next day, the formula was changed to short peptide EN nutrient (Peptisorb Liquid, Wuxi, China). After 3-5 days post-operation, patients with anal exhaust started to receive (LESKON, Xi'an, China), and the daily nutrient flow rate and pump volume were as described16. Both groups were treated for 7 days (Figure 1).

Evaluation Criteria

Nutritional status

Upper serum from the fasting venous blood (5.0 ml) was collected from both groups on the day of the surgery and 7 days after the surgery. Levels of preprotein, albumin, and hemoglobin were detected by Enzyme-Linked Immunosorbent Assay (ELISA)[17].

Short-form 36 health survey scale (SF-36)

Short-form 36 (SF-36) health survey scale was used to evaluate patients' quality of life before and after the treatment. The scale took into account 8 dimensions: all-round health, physiological function, physiological ability, body pain, vitality, social function, emotional function and spirit health, with a total of 36 items. The total score of SF-36 and the scores of each dimension were converted into the percentage system for easy understanding. A higher score indicated better quality of life[18].

Statistical Analysis

SPSS 18.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for data analysis. Continuous variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR), based on the normality of distribution, assessed by the Shapiro-Wilk test. The statistical significance of differences in continuous variables between the intervention and control groups was assessed using independent *t*-tests for normally distributed data and Mann-Whitney U tests for non-normally distributed data. Categorical variables were reported

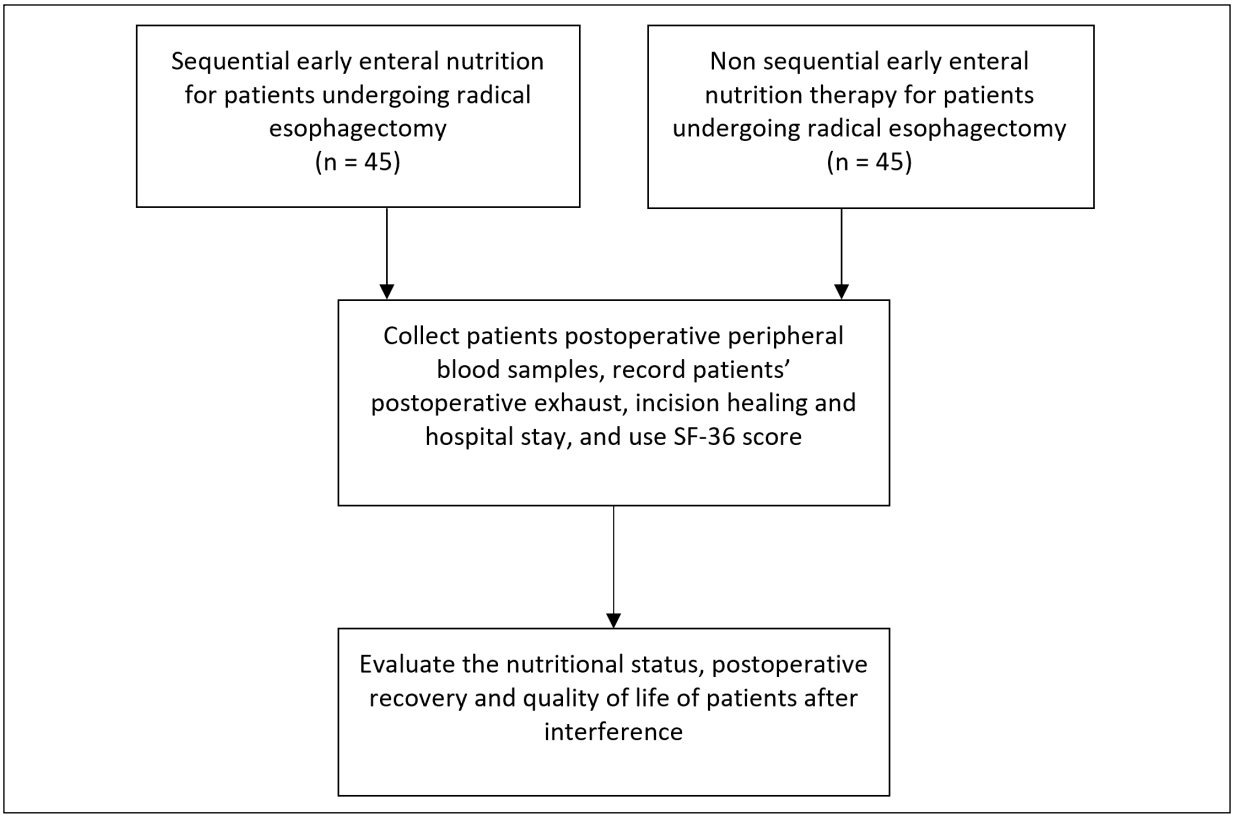

Figure 1. Flow chart diagram of the nutritional support therapy.

as frequencies and percentages using Chi-square tests. $p<0.05$ indicated statistical significance.

Results

Comparison of Nutritional Status Between the Two Groups Before and After the Nutritional Intervention

Table II shows no significant difference in pre-protein, hemoglobin and albumin levels between the two groups before the nutritional intervention ($p<0.05$). After the intervention, the above indexes were significantly higher in both groups ($p<0.05$), and pre-protein, hemoglobin and albumin were markedly higher in the Test group compared to the control group ($p<0.05$). This shows that the nutrition absorption of patients after the ESEN intervention is better.

Comparison of Recovery After Nutritional Intervention Between the Two Groups

As shown in Table III, exhaust, incision healing, and hospitalization time of the Test group after the intervention were dramatically lower than those of the control group ($p<0.05$).

Comparison of SF-36 Scores Between The Two Groups Before and After The Intervention

There was no statistical diversity in the comparison of SF-36 scores and total scores between the two groups before the intervention, as shown in Table IV ($p>0.05$). After the intervention, the scores of all dimensions and total scores of SF-36 in the two groups were significantly higher than those before the intervention ($p<0.05$), and the scores of all dimensions and total scores in the Test group were higher than those in the control group ($p<0.05$).

Discussion

Postoperative patients with esophageal cancer often suffer from malnutrition due to difficulties in eating. Additionally, surgical stress and rehydration often cause high metabolism and decreased immune function. Early enteral nutrition support can improve patients' immunity, reduce postoperative adverse reactions, and shorten the postoperative recovery process by promoting the restoration of gastrointestinal function and replenishing energy, which is important for improving the prognosis of these patients[19,20]. As opposed to enteral nutrition with a single whole protein nutrient, ESEN takes into account the patient's intestinal tolerance and nutrient absorption. Therefore, this mode of nutritional support may be more compatible with postoperative nutritional requirements of postoperative patients with esophageal cancer[21,22].

The results of our study indicated that while the serum levels of pre-protein, albumin and hemoglobin in the two groups increased after the postoperative intervention, the ESEN nutritional support

Table II. The contrast of nutritional status between the two groups before and after interference.

Category	Pre-protein (mg/L)		Hemoglobin (g/L)		Albumin (g/L)	
	Before interference	After interference	Before interference	After interference	Before interference	After interference
Test group (n=45)	105.56±11.37	118.04±10.31*	94.60±6.64	110.45±8.07*	24.39±5.10	36.61±4.27*
Contrasted group (n=45)	104.94±12.20	110.26±12.81*	95.18±5.98	103.10±9.65*	23.48±4.51	31.05±4.61*
t	0.248	3.174	-0.432	3.914	0.895	5.931
p	0.805	0.002	0.667	<0.001	0.373	<0.001

*Indicates that compared with the same group before interference, $p < 0.05$.

Table III. Comparison of recovery after interference between the two groups (day).

Category	Exhaust	Incision healing	Hospitalization time
Test group (n=45)	2 (2.3)	5 (4.5)	9 (8.9)
Contrasted group (n=45)	3 (3.3)	6 (6.7)	11 (10.12)
t	-4.260	-6.302	-5.644
P	<0.001	<0.001	<0.001

Table IV. Comparison of SF-36 scores between the two groups before and after interference (points).

Category		Test group (n=45)	Contrasted group (n=45)	*t*	*p*
All-round health	Before interference	59.64±11.05	59.51±11.24	0.057	0.955
	After interference	78.71±8.31*	70.62±7.31*	4.903	<0.001
Physiological function	Before interference	60.44±6.34	60.27±8.19	0.115	0.909
	After interference	77.22±7.40*	68.22±7.28*	5.815	<0.001
Physiological ability	Before interference	58.82±7.74	58.07±7.37	0.474	0.636
	After interference	80.36±5.81*	71.51±6.36*	6.889	<0.001
Body pain	Before interference	57.31±7.35	56.53±7.01	0.514	0.609
	After interference	76.71±6.55*	68.67±8.20*	5.144	<0.001
Vitality	Before interference	63.44±8.97	62.58±11.35	0.402	0.689
	After interference	77.82±11.3*	70.67±10.09*	3.168	0.002
Social function	Before interference	65.42±10.15	65.20±9.67	0.106	0.916
	After interference	77.58±10.14*	69.33±11.80*	3.555	0.001
Emotional function	Before interference	64.38±11.45	64.89±9.46	-0.231	0.818
	After interference	79.69±10.14*	71.49±9.21*	4.016	<0.001
Spirit health	Before interference	56.73±8.32	57.38±8.94	-0.354	0.724
	After interference	79.11±10.75*	69.98±9.74*	4.223	<0.001

*Indicates that compared with the same group before interference, $p < 0.05$.

was associated with significantly higher levels of these indicators than those in the control group. These results suggest better nutrition absorption after ESEN intervention, which is similar to the results of Ding et al[23]. We may speculate that the recovery of intestinal mucosal absorption function of patients after the operation is a dynamic process. At first, it is fragile, with insufficient digestive enzyme secretion and poor protein absorption. Therefore, the amino acid formula can be directly absorbed at that stage. Subsequently, the secretion of digestive enzymes gradually increases, leading to the ability to absorb short peptide nutrients with a relatively simple protein structure. Postoperative exhaust, incision healing, and length of hospitalization in the patients who received ESEN support were significantly lower than those of the control group, and the scores and total scores of SF-36 were higher. Our results are in agreement with the results of Huang et al[24]. We hypothesize that the recovery of gastrointestinal function and physical function cannot be separated from energy and protein. After the ESEN intervention, patients' nutrition absorption is faster, immunity recovery is faster, and endogenous infection can be effectively reduced. Therefore, postoperative gastrointestinal function recovery and wound healing in patients receiving ESEN are faster, ultimately leading to markedly improved physiological well-being. In addition, adequate nutrition itself can reduce postoperative adverse psychological reactions. In the process of ESEN intervention, short peptide enteral nutrition can improve patients' microcirculation, repair the intestinal barrier damaged after the anesthesia, improve an overall postoperative experience, reduce postoperative fear, and improve patients' quality of life[25]. In summary, the postoperative ESEN intervention for esophageal cancer patients is associated with mild nutritional support and good absorption. The postoperative nutritional status of patients is better, the gastrointestinal function and wound recovery are faster, and the overall quality of life is significantly improved.

Limitations

This is a retrospective analysis with a small sample size and selection bias. There are few observation indicators, especially laboratory indicators; Additionally, there is a lack of follow-up data. Further clinical multicenter studies with large sample sizes are needed to verify our results.

Conclusions

Sequential early enteral nutrition may be used for patients who undergo chemotherapy after esophageal cancer surgery to promote their early recovery and improve their quality of life and nutritional status.

Conflict of Interest

There is no conflict of interest between all authors.

Informed Consent
Patient informed consent was waived because of the retrospective nature of the study.

Authors' Contributions
HS conceived and designed the study. SW, GA, and GZ collected the data and performed the analysis. HS was involved in writing the manuscript of the study. XZ was responsible for the integrity of the study. All authors have read and approved of the final manuscript.

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Ethics Approval
The Ethics Committee of Gansu Provincial Cancer Hospital approved this study on April 30th, 2020, with the No. P202004150014.

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