Original Article

A randomized controlled trial of oral nutritional supplementation versus standard diet following McKeown minimally invasive esophagectomy in patients with esophageal malignancy: a pilot study

Hounai Xie[1], Xiankai Chen[1], Lei Xu[1], Ruixiang Zhang[1], Xiaozheng Kang[1], Xiufeng Wei[2], Yafan Yang[1], Yin Li[1]

[1]Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [2]Department of Thoracic Surgery, Chuiyangliu Hospital Affiliated to Tsinghua University, Beijing, China

Contributions: (I) Conception and design: H Xie; (II) Administrative support: Y Li, R Zhang; (III) Provision of study materials or patients: X Chen; (IV) Collection and assembly of data: X Wei; (V) Data analysis and interpretation: L Xu, X Kang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yin Li. Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 17 Nanli, Panjiayuan, Chaoyang District, Beijing 100021, China. Email: liyin_thorax@163.com.

Background: Body weight loss (BWL) following esophagectomy is a common complication in esophageal cancer (EC) which represents a deterioration in quality of life (QoL) and poor long-term prognosis. A pilot randomized controlled study was initiated to evaluate the feasibility, safety, and efficacy of a short-term oral nutritional supplementation (ONS) on postoperative BWL and QoL in patients undergoing esophagectomy.

Methods: Patients enrolled in this study were randomly divided into two different groups: the intervention group which received oral nutritional intervention (300 mL/day for 4 weeks) and the control group which received standard diet alone. Participants were assessed at discharge and 1, 3, and 6 months following discharge for BWL and QoL. At the same time, the data of clinical baseline characteristics, nutrition-related complications, and feasibility were prospectively collected and analyzed.

Results: A total of 77 patients were enrolled in this study. However, owing to severe postoperative complications and discontinuation of the program, 33 participants in the ONS group and 31 participants in the control group were eligible for final analysis of body weight change and QoL. Significant differences in percentage of BWL (%BWL) between the two groups were discovered at 3 and 6 months follow-up: participants in the ONS group had lower %BWL than those in the control group (P=0.024; P=0.025, respectively). There were significant differences in body mass index (BMI) loss between the two groups. At 1 month, QoL was significantly improved in the ONS group (P=0.031); however, no differences of QoL were noticed at 3 and 6 months. Compared with the control group, ONS improved the physical function and role function and eased the symptom of fatigue (P=0.014, P=0.030, and P=0.008, respectively). It was also noted that ONS increased the nutrition-related complications compared to the standard diet (50% *vs.* 42.9%), although the difference was not statistically significant (P=0.647).

Conclusions: This pilot study indicated that addition of ONS was feasible, safe, and might prevent the loss of body weight and BMI and have a positive impact on the QoL in esophagectomy patients. The effectiveness of ONS requires further confirmation in an appropriately powered study.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2100045303.

Keywords: Oral nutritional supplementation (ONS); standard diet; McKeown minimally invasive esophagectomy; early oral feeding

Submitted Sep 16, 2021. Accepted for publication Oct 29, 2021.
doi: 10.21037/atm-21-5422
View this article at: https://dx.doi.org/10.21037/atm-21-5422

Introduction

Esophageal cancer (EC) is the most common malignant tumor of the digestive tract and has been reported to globally cause a remarkable number of deaths annually (1,2). For patients with EC, resection of EC combined with regional lymph node dissection is the most effective treatment (3). The surgery for EC is one of the most complex gastrointestinal surgeries, which has a high incidence of postoperative complications, at about 20–80% (4). The enhanced recovery after surgery (ERAS) principle was first applied in abdominal surgery, and has been successfully introduced into esophageal surgery, where it has achieved great success (5). ERAS programs can hasten postoperative recovery of patients and shorten hospital stay without increasing mortality and morbidity, through optimizing multimodal interventions during the perioperative period (6). Appropriate and effective nutritional support play a key role in the recovery of patients undergoing esophagectomy (7). In the past few years, early oral feeding has become the standard care for all types of abdominal surgery (8). The timing of oral feeding in esophageal surgery is still controversial. However, multiple medical teams around the world have confirmed the safety and feasibility of early oral feeding after esophagectomy (9-11). Early oral feeding is an important aspect in ERAS programs that can improve patient outcomes and decrease length of hospital stay (LOS) and the incidence of complications.

Body weight loss (BWL) is a common complication in EC which represents a deterioration in quality of life (QoL) and poor prognosis (12). A study by Deans *et al.* showed that 83 (83%) patients had BWL at the time of diagnosis with almost half of these patients losing 10% or more of their pre-illness body weight (13). Patients with esophageal malignancy not only experience the systemic effects of the disease on their nutritional status (for example, anorexia and altered protein metabolism), but also are affected by the local effects of the tumor on the upper digestive tract (14). Hyper-catabolism associated with inflammation due to surgical stress and reduced food intake and alteration of gastrointestinal digestion function due to alimentary reconstruction all result in malnutrition (15). At the same time, the side effects of neoadjuvant and postoperative adjuvant therapy increase the incidence of malnutrition. A systematic review showed that the most marked BWL mainly occurred 6 months after esophageal surgery, which was about 5–12% lower than the baseline level (15). Martin *et al.* found that more than half of the patients lost more than 10% of their body weight and 1 in 5 lost more than 20% (16). Therefore, it remains a great challenge for clinicians and patients to improve nutritional status and suppress weight loss following esophagectomy.

Postoperative oral nutritional supplementation (ONS) is a key to improving daily caloric and protein intake following oncologic surgery. Multiple clinical studies have shown that ONS can improve the nutritional status of cancer patients, improve tolerance to radiotherapy and chemotherapy, and even prolong the survival time and improve the QoL of cancer patients (17,18). According to Baldwin *et al.*, in their study involving 1,414 cancer patients, ONS could increase body weight and energy intake, and impact emotional state, dyspnea, and appetite of cancer patients (19).

However, there have been few studies on the effects of ONS which have focused on patients undergoing esophagectomy for EC. In our study, all patients could tolerant the early oral feeding because of the cervical manual anastomose at the first postoperative day. Therefore, we conducted a pilot single-center prospective, randomized, controlled clinical trial to examine the effect of oral nutritional support in patients with esophagectomy, to assess the feasibility of conducting a subsequent appropriately powered randomized clinical trial (RCT). Our primary hypothesis was that patients who received early, continuous ONS would have decreased BWL after esophagectomy compared with the control group. Perioperative and histopathological outcomes, nutritional status including body mass index (BMI), and QoL were also studied.

We present the following article in accordance with the CONSORT reporting checklist (available at https://dx.doi.org/10.21037/atm-21-5422).

Methods

Study design

This was a prospective randomized, single-blind, pilot controlled clinical trial to assess the efficacy of ONS on

BWL after esophagectomy for EC. This clinical trial was conducted at the Department of Thoracic surgery, Cancer Hospital of Chinese Academy of Medical Sciences (Beijing, China). The nature of this study made it impossible to use a double-blind method. Therefore, the clinical dietitians who were not involved in patient care were responsible for collecting clinical data with the intention of reducing bias. This trial was registered with the Chinese Clinical Trial Registry Network (ChiCTR2100045303).

Participants and setting

This trial recruited patients with EC undergoing McKeown minimally invasive esophagectomy (MIE) with cervical hand-sewn anastomosis between August 2020 and January 2021. Patients were eligible for this study if they satisfied the following inclusion criteria: histologically confirmed curable esophageal carcinoma; aged 18–78 years; clinical T1-3, N0-2, and M0 disease; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; adequate organ function; suitability for early oral feeding; written informed consents were provided by all patients before they were randomly assigned. The preoperative exclusion criteria were as follows: inability to perform McKeown MIE; acute or unstable cardiac conditions, cardiac failure (New York Heart Association functional classes III and IV), or other organ failure. The postoperative exclusion criteria were: inability to tolerate oral feeding owing to irritating cough; combined organ resection; exploratory surgery; more than 24 h stay in the intensive care unit (ICU).

Recruitment and ethics

Potential participants were interviewed by a member of the surgical team regarding whether they were interested in joining our clinical trial. We explained the study in detail and provided them participant information material. Then, those who agreed to participate were required to provide written informed consent.

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethical Review Committee of Cancer Hospital of Chinese Academy of Medical Sciences (21/058-2729). All patients were enrolled after receiving detailed explanation of the study protocol and after they or their family members had provided written informed consent.

Randomization

Computer randomization software which SPSS generated random number, was used to randomly allocate participants (1:1 ratio) to 1 of 2 treatment groups (the ONS group and the control group) within 1 week before surgery. Computerized randomization lists were created, and the results were placed in sealed opaque envelopes by individuals not involved in the trial. Based on the treatment allocation numbers generated on the computer, the participants entered the trial in order. The dietitian was the only researcher who was aware of the nutritional intervention program of participants. The main statisticians and clinicians were unaware of the group assignments.

Standard postoperative care

Participants enrolled in our trial all received McKeown MIE with 2- or 3-field lymph node dissection of which cervical hand-sewn anastomosis was the key step. All the surgeries were performed by 1 surgical team led by 1 author (YL). Both groups were treated without nasojejunal feeding tube and nasogastric tube. Parenteral nutrition via a central line was administered and a mixed dextrose amino acids fatty emulsion was transfused venously to provide kilocalories. The detailed nutritional support protocol is shown in *Table 1*. Harris-Benedict formula were performed to estimate non-protein energy requirements for post-operative participants by dieticians. We used Elia to calculate protein requirement for nitrogen.

At the first postoperative day (POD), participants were allowed to drink sips of liquids while being observed for symptoms of aspiration, including coughing and throat clearing. If none of those signs were observed, participants were encouraged to consume food. The experienced clinicians offered careful guidance of oral feeding and dieticians provided nutrition education. At POD 1, liquid foods such as juice, milk, and porridge were admitted. At POD 2, soft solid foods and semiliquid food such as rice, eggs, and noodles were administered. At POD 3, normal food (well cooked vegetables and meat or some common types of fruit such as bananas, oranges, peaches) were permitted. The deficit of required energy could be compensated by parenteral nutrition. The target food intake was 200–300, 400–500, 600–800, and 900–1,000 mL, respectively at POD 1, POD 2, POD 3, and POD4. From POD 5, participants were required to be able to consume

Table 1 Nutritional support pathway

POD	ONS group	Control group
1	Energy of 1,000–1,500 kcal and acid of amino acid of 1.5 g/kg supplied by PN; oral intake of liquid food 200–300 mL	
2	Energy of 800–1,000 kcal and amino acid of 1.0 g/kg supplied by PN; oral intake of soft solid foods and semiliquid food 400–500 mL	
3	Energy of 500–800 kcal and amino acid of 1.0 g/kg supplied by PN; oral intake of normal food (well cooked vegetables and meat or some common types of fruit) 600–800 mL	
4	The PN was stopped; oral intake of normal food 900–1,000 mL	
5-	Oral intake of normal food at least 1,000 mL; ONS 300 mL via oral intake	Oral intake of normal food
Discharge	Oral intake of normal food at 1,200–1,500 mL; ONS 300 mL via oral intake	Oral intake of normal food
	Follow up: 1, 3, and 6 months after discharge	

POD, postoperative day; ONS, oral nutrition supplement; PN, parenteral nutrition.

at least 1,000 mL food orally when parenteral nutrition was stopped, otherwise they could not get enough energy from oral feeding. The discharge criteria were the presence of normal vital signs, ability to consume a normal diet (oral take 1,200–1,500 mL), no signs of a postoperative complication that needed to be treated at the hospital, ability to ambulate without assistance, adequate pain tolerance on oral analgesia, and removement of surgical drainages.

Intervention and control

The participants of the ONS group received 300 mL (1.5 kcal/mL) nutritional supplement, in addition to their standard diet, for 4 weeks, beginning from the day that their total intake was at least 1,000 mL. The amount of supplement consumed was measured with a measuring cup and recorded in a notebook completed by the participants. Meanwhile, the control group received regular diet (1,400–1,600 kcal/day) alone. Participants recorded their daily dietary intake using a simple dietary survey leaflet throughout the study period. The special dietitian and clinician was responsible for monitoring participants' adherence and addressing commonly encountered issues by telephone call or clinic visit after discharge.

Data collection

The clinical baseline data was collected including patient and tumor characteristics, and operative and postoperative details. In this study, we selected the percentage of body weight loss (%BWL) between the patient's presurgical body weight and that at different time points after discharge as the primary endpoint. The measure determined whether or not the trial would be initiated and an appropriately powered definitive trial would be possible. Body weight was measured to the nearest 0.1 kg with the patient dressed but without shoes or heavy outerwear. Height was measured to the nearest 0.5 cm with the patient barefoot. The BMI was calculated as weight (kg)/height (m^2).

The secondary outcomes were the change of BMI, compliance to ONS, nutrition-related adverse events, and QoL. In addition, the indicators of body composition cannot be measured because of the damage of measuring device.

Compliance was defined as the proportion of consumed dose to target dose. Adherence to ONS was based on the doses recorded in a diary. The degree of compliance with ONS was based on the proportion of participants' actual consumption to prescribed dose. According to the previous observation, we designed a set of questionnaires for participants to assess adherence to ONS and explore potential reasons for noncompliance. The questionnaire items were as following: presence of diarrhea, flatulence, nausea or vomiting, bellyache or stomach pain, flavor dislike, continuous satiety, and subjectively no need for the supplements (*Table 2*). The use of specific questions was initially based on the most frequently reported reasons for low compliance among cancer patients in previous studies, as well as on the main problems patients encounter postoperatively that could affect their nutritional intake (20,21).

Adverse events were recorded according to the Common Terminology Criteria of the National Cancer Institute (version 4.0; https://evs.nci.nih.gov/ftp1/CTCAE/

Table 2 ONS compliance questionnaire used in the study

During the last 4 weeks, which of the following symptoms/reasons kept you from consuming the prescribed amount of ONS		
Today's date: XXX/XXX/XXX		
Patients' name: XXX	Age: XXX	Gender: XXX
Patient's ID#: XXX		
1. Did you have the flatulence?		Yes/No
2. Did you have the diarrhea?		Yes/No
3. Did you have bellyache or stomach pain?		Yes/No
4. Did you have nausea or vomiting?		Yes/No
5. Did you like this flavor?		Yes/No
6. Were you hungry for the following meal after ONS? (satiety)		Yes/No
7. Did you think that ONS was necessary for you?		Yes/No
8. Other reasons (please describe):		
INSTRUCTION: Fill in personal information in detail. Answer every question by ticking "Yes" or "No".		

ONS, oral nutrition supplement.

CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf). The European Organization for Research and Treatment of Cancer questionnaires-C30 (EORTC QLQ-C30; https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-QLQ-C30-English.pdf) were used to assess QoL at baseline and 1, 3, and 6 months after discharge.

Statistical analysis

As this was a feasibility study, we selected this sample size for the sake of enabling a sensible estimation of the quantities of interest without exposing a large number of participants to the full range of the experimental process. The pilot study recruiting 60 patients would give us enough information on the size of effect and recruitment rate to plan an adequately powered study. In cases of sever adverse events or lack of funds, the study will be discontinued.

We performed the Shapiro-Wilk test to confirm whether the data satisfied the normality of the distributions. The χ^2 and Student's *t*-tests were used, as appropriate, to assess the differences between groups in participant demographics. Fisher's exact test for categorical variables and two-sample *t*-test for numerical variables were used to assess differences between the two groups. Continuous variables not normally distributed were analyzed by nonparametric tests. Differences in values, including those of percent change in weight, percent change in BMI, and blood chemistry data between the two groups were evaluated using *t*-tests. The EORTC QLQ-C30 was applied to analyze differences between the groups using the Mann-Whitney U test method. All statistical analyses were carried out with the software SPSS, version 24.0 (IBM Corp., Armonk, NY, USA). A two-sided level P value ≤0.05 was considered statistically significant.

The final data analysis was performed using modified intention-to-treat set, which excluded participants` information with poor compliance or lost follow up.

Results

Participant characteristics

Between September 2020 and January 2021, a total of 118 patients who were diagnosed with EC in this hospital were screened for eligibility. We excluded 41 patients for the following reasons: insufficient organ function (n=5); not a candidate for McKeown MIE (n=15); age >78 years old (n=5); refused to participate (n=6); unresectable disease (n=6); and intolerance of early oral feeding (n=4). Thus, 77 patients were randomly assigned to the ONS group and control group. However, one patient in the ONS group and 3 patients in control group exited this study early due to complications, which included anastomotic leak (n=3) and severe pneumonia (n=1). During the follow up

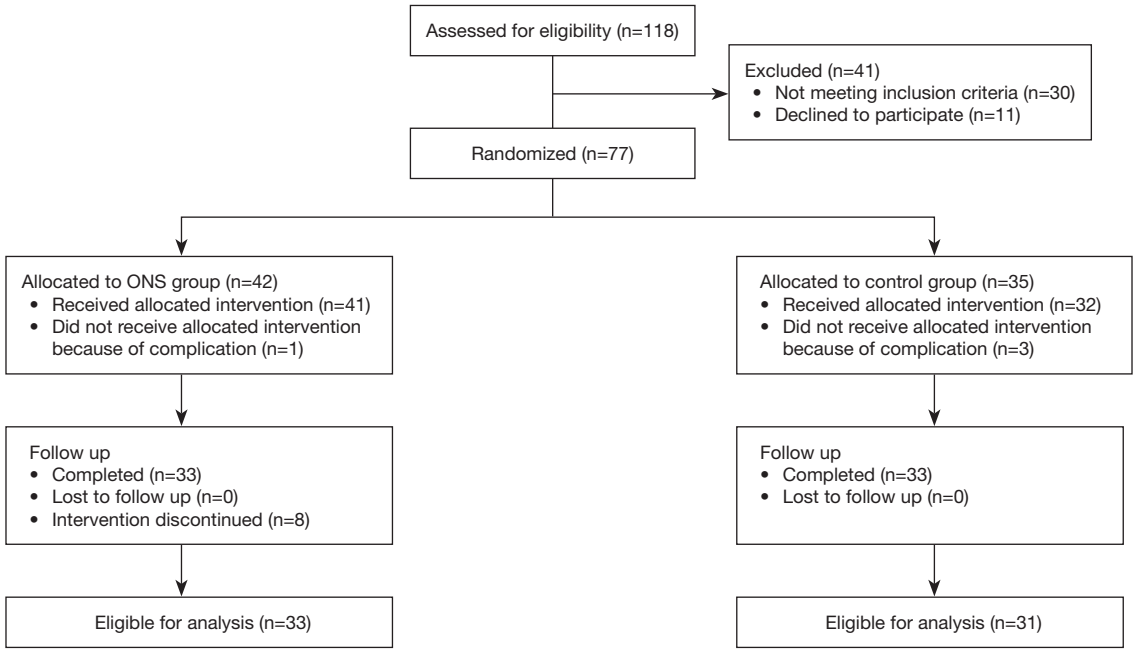

Figure 1 Flowchart. ONS, oral nutrition supplement.

period, 8 participants were excluded from the final analysis due to noncompliance. Finally, 33 patients in the ONS group and 31 patients in the control group were analyzed for BWL, BMI change, and QoL. The flow chart of this study is shown in *Figure 1*. The demographics of these participants are summarized in *Table 3*. There were no significant differences in age, gender, weight, BMI, receipt of neoadjuvant chemotherapy, histology characteristic, and preoperative comorbidity between the two groups.

Table 4 shows the surgical and postoperative outcomes. There were no significant differences in surgical time, pathologic staging, length of hospital stay (LOS), unscheduled readmission within 30 days, 30-day mortality, 90-day mortality, and postoperative adjuvant therapy between the two groups. All participants underwent MIE. The incidence of overall postoperative complication in intervention group was 31.7% compared to 36.1% in control group with no sign of significant difference (P=0.683). There was no significant difference in the severity of postoperative complications in terms of Clavien-Dindo classification.

Changes in body weight and BMI over time

The BWL and BMI change are shown in *Table 5*. Compared with pre-operation, 6 (9.4%) participants, 26 (40.6%) participants, and 31 (48.4%) participants had more than 10% BWL at 1, 3, and 6 months respectively. The mean rate of weight loss was greatest at 1 month post discharge (4.52%±3.12% in the ONS group; 5.92%±4.88% in the control group). From 1 to 3 months, the average rates of weight loss were 3.37%±4.25% in the ONS group and 5.14%±3.36% in the control group. The rate of average weight loss was least from 3 to 6 months (0.80%±3.05% in ONS group; 1.01%±2.74% in control group). Overall weight loss from pre-operation to the follow-up points were not significantly different according to whether participants had neoadjuvant treatment or not (P=0.393, P=0.970, P=0.749, at 1, 3, and 6 months, respectively).

As shown in *Figure 2*, there were no significant differences in the body weight change, %BWL, or BMI change at discharge and at 1 month. At 1 month after discharge, participants in the ONS group had lost on average 3.16 kg less than the 4.09 kg lost in the control group [P=0.206, 95% confidence interval (CI): 0.53 to 2.39]. The mean differences were 1.89 and 2.0 kg between the ONS group and control group at 3 months and at 6 months, respectively (P=0.051, 95% CI: −0.01 to 3.79; P=0.062, 95% CI: −0.11 to 4.07). We merely discovered a trend of difference rather than statistical significance. On the other hand, the %BWL was significantly lower in the ONS group than in the control group at 3 months

Table 3 Patient characteristics at baseline (before surgery)

Variable	ONS group (n=42)	Control group (n=35)	P value
Age (years)	61.57±8.45	63.06±5.79	0.381
Gender, n (%)			0.636
Male	33 (78.6)	29 (82.9)	
Female	9 (21.4)	6 (17.1)	
Height (cm)	169.62±7.76	169.31±7.89	0.865
Weight (kg)	66.83±12.01	67.21±10.81	0.883
BMI before surgery (kg/m^2)	23.12±3.16	22.94±5.10	0.149
NRS2002, n (%)			0.683
≥3	4 (9.5)	2 (5.7)	
<3	38 (90.5)	33 (94.3)	
ECOG performance status, n (%)			0.290
0	15 (35.7)	7 (20.0)	
1	25 (59.5)	25 (71.4)	
2	2 (4.8)	3 (8.6)	
Preop comorbidity, n (%)			0.503
Yes	22 (52.4)	21 (60.0)	
No	20 (47.6)	14 (40.0)	
Neoadjuvant treatment, n (%)			0.191
Yes	28 (66.7)	28 (80.0)	
No	14 (33.3)	7 (20.0)	
Histology, n (%)			0.831
SCC	39 (92.9)	32 (91.4)	
AC	2 (4.8)	1 (2.9)	
Others	1 (2.4)	2 (5.7)	
cT stage, n (%)			0.783
T1	10 (23.8)	5 (14.3)	
T2	4 (9.5)	3 (8.6)	
T3	27 (64.3)	26 (74.3)	
T4	1 (2.4)	1 (2.9)	
cN stage, n (%)			0.943
N0	19 (45.2)	14 (40.0)	
N1	19 (45.2)	18 (51.4)	
N2	2 (4.8)	2 (5.7)	
N3	2 (4.8)	1 (2.9)	
cM stage, n (%)			–
M0	42 (100.0)	35 (100.0)	
M1	0	0	
Location of tumor, n (%)			0.228
Upper	6 (14.3)	2 (5.7)	
Middle	16 (38.1)	20 (57.1)	
Lower	20 (47.6)	13 (37.1)	
Preoperative blood test			
Total protein	64.69±5.54	66.74±5.21	0.136
Albumin	38.74±3.22	39.65±3.33	0.270
Prealbumin	24.17±4.24	24.51±4.56	0.753
Transferrin	220.32±33.71	223.92±33.27	0.670
Hb	128.91±14.12	132.90±16.76	0.443

ONS, oral nutrition supplement; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.

(7.77%±4.38% *vs.* 10.63%±5.47%, P=0.024, 95% CI: −5.32 to −0.39). A significant difference of %BWL between the two groups was also discovered at 6 months (8.52%±4.99% *vs.* 11.52%±5.46%, P=0.025, 95% CI: −5.62 to −0.39). At 1 month after discharge, the mean difference in BMI between the control and ONS groups was 1.13 kg/m^2 (P=0.102, 95% CI: −0.36 to 0.86). The BMI change was significantly lower in participants with additional oral nutritional supplement than those without at 3 months and 6 months (P=0.024, 95% CI: 0.33 to 0.11; P=0.026, 95% CI: 0.36 to 0.1).

Comparison of compliant and noncompliant patients

The rate of compliance was recorded at 4 weeks after ONS initiation. Participants who were able to consume at least 3/4 of the prescribed quantity were considered compliant, whereas those who did not achieve the recommended goal were considered noncompliant, according to a previous report (22). The compliance for oral nutritional supplement was explored in 41 participants. The mean treatment compliance rate for ONS was 71.1±21.8,

with a median value of 76.3. However, 33 of 41 (80%) participants achieved the goal with good compliance. The most common barriers were diarrhea, continuously satiety, and flatulence (*Table 6*). The percentage of non-compliant participants with diarrhea was significantly higher than compliant patients (75% *vs.* 12.1%, P=0.001). Flatulence was also a vital factor which influenced the low compliance, showing a significant difference compared to compliant participants (62.5% *vs.* 15.2%, P=0.013). Other factors such as insufficient medication guidance, tedious medication process, and poor memory could also diminish compliance; nevertheless, no statistically significant differences were observed.

Nutrition-related complication

As shown in *Table 7*, 42 and 35 participants in the ONS and control groups, respectively, were included in the safety analyses. The nutrition-related adverse events in the two groups were similar (50.0% *vs.* 42.9%, P=0.647). A participant in the ONS group and 3 participants in control group had Clavien-Dindo grade 3 complications in hospital. No Clavien-Dindo grade 3 and worse complications were reported in each group after discharge. A dietitian was available to offer regular dietary guidance to avoid the nutrition-related complications, which included a little each time but often, chewing food well, avoiding cold and greasy meals, meals rich in carbohydrates and protein, avoiding a simple liquid diet, and so on. Especially for participants in ONS group, we encouraged them to drink slowly, keep the liquid warm, and mix it with sugar or juice. To manage existing complications, we prescribed appropriate medications such antidiarrheal, anti-acids, and so on.

QoL assessment

To evaluate whether the oral nutritional supplement improved the QoL of postoperative patients with esophagectomy, the EORTC QLQ-C30 was used as the follow-up questionnaire (*Table 8*). In order to allow the scores of each field be compared with each other, the linear transformation of extreme difference method was further used to convert the rough score into the standard score (SS) with the value between 0 and 100. In the QLQ-C30 scale, it is clearly stipulated in the scoring rules: the higher the score in the functional field and the overall health status field, the better the functional status and QoL; the higher the score in the symptom field, the worse of the QoL. There were no significant differences in baseline QoL scores between the two groups. At 1 month after discharge, the scores of physical function, role function, and global health status were significantly higher in the intervention group than in participants in the control group (P=0.014, P=0.030, and P=0.031, respectively). The participants in the ONS group reported statistically significantly less problems with fatigue than those in the control group (P=0.008). No significant differences of QoL were discovered between the two groups at 12 and 20 weeks.

Discussion

Anorexia and decreased food intake are common clinical manifestations in cancer patients. Patients with EC often have decreased food intake due to impaired swallowing function or eating obstruction. As mentioned before, surgery-based comprehensive treatment including radiotherapy and chemotherapy have a serious impact on the nutrition of patients with EC (12). BWL is one of the major clinical manifestations of malignant tumors, which is significantly related to the clinical outcome of tumor patients (23). More than 50% of EC patients experience at least a 10% BWL (24). Accordingly, nutritional intervention is vital to achieve better clinical outcomes. Most prior studies have focused on the benefit of home enteral nutrition and home parenteral nutrition (HPN) in EC patients undergoing esophagectomy (25-27). To our acknowledge, this study was the first RCT to compare a planned program of oral nutritional supplement to usual care in EC patients. The major findings were that ONS was not only safe, feasible, and acceptable to patients, but also that it could attenuate weight loss and improve QoL after esophagectomy.

BWL diminishes postoperative QoL, impairs the immune function, and increases the risk of morbidity and mortality (28). Several years ago, a randomized trial of 54 patients comparing home enteral nutrition for 6 weeks with standard diet was initiated by the Department of Surgery, University Hospital of Leicester. They reported that participants in the control group had lost on average 3.9 kg more than those in the intervention group (95% CI: 1.6 to 6.2) at 6 weeks and these differences remained evident at 3 months (mean difference 2.5 kg) and at 6 months (mean difference 2.5 kg) (29). In our prospective study, despite being offered ONS, the BWL in patients with esophagectomy remained extremely common. However, the mean difference of BWL between the two groups was 1.89 and 1.97 kg,

Table 4 Postoperative and histopathological outcomes

Variable	Interventional group (n=42)	Control group (n=35)	P value
Hospital stay (days)	13.17±5.76	12.80±7.67	0.816
ICU stay, n (%)	2 (4.9)	2 (5.6)	1.000
Operation time (min)	225.40±38.32	227.74±49.69	0.962
Surgery bleeding (mL)	77.86±28.50	85.43±32.75	0.322
Unscheduled readmission within 30 d, n (%)	1 (2.4)	2 (5.7)	0.588
30-day mortality, n (%)	0	0	–
90-day mortality, n (%)	0	0	–
Anastomotic leak, n (%)	1 (2.4)	2 (5.7)	0.596
Dilatation of gastric tube, n (%)	3 (7.1)	3 (8.6)	1.000
Pneumonia, n (%)	4 (9.5)	6 (17.1)	0.498
Pleural effusion, n (%)	2 (4.8)	4 (11.4)	0.402
Atelectasis, n (%)	2 (4.8)	5 (14.3)	0.235
Respiratory failure, n (%)	0	1 (2.9)	0.455
Myocardial arrhythmia, n (%)	4 (9.5)	1 (2.9)	0.369
Heart failure, n (%)	0	1 (2.9)	0.455
Recurrent laryngeal nerve paralysis, n (%)	3 (7.1)	4 (11.4)	0.695
Patients with any complication, n (%)	13 (31.7)	13 (36.1)	0.683
Clavien-Dindo grading system, n (%)			
Grade I	4 (9.8)	3 (8.3)	1.000
Grade II	8 (19.5)	6 (16.7)	0.777
Grade III	1 (2.4)	3 (8.3)	0.335
Grade IV	0	0	–
CRT, n (%)			0.183
Yes	13 (31.0)	16 (45.7)	
No	29 (69.0)	19 (54.3)	
Surgical procedure, n (%)			–
VATS + laparoscopic surgery	42 (100.0)	35 (100.0)	
Open surgery	0	0	
McKeown, n (%)	42 (100.0)	35 (100.0)	–
Radicality, n (%)			–
R0	42 (100.0)	35 (100.0)	
R1	0	0	
pTNM stage, n (%)			
PT stage			0.614
T0	6 (14.3)	4 (11.4)	

Table 4 (*continued*)

Table 4 (*continued*)

Variable	Interventional group (n=42)	Control group (n=35)	P value
T1	12 (28.6)	13 (37.1)	
T2	10 (23.8)	6 (17.1)	
T3	10 (23.8)	11 (31.4)	
T4	4 (9.5)	1 (2.9)	
pN stage, n (%)			0.936
N0	28 (66.7)	22 (62.9)	
N1	7 (16.7)	7 (20.0)	
N2	5 (11.9)	5 (14.3)	
N3	2 (4.8)	1 (2.9)	
pM stage, n (%)			–
M0	42 (100.0)	35 (100.0)	
M1	0	0	
Pathologic stage, n (%)			
0	6 (14.3)	3 (8.6)	0.834
I	11 (26.2)	9 (25.7)	
II	12 (28.6)	14 (40.0)	
III	10 (23.8)	7 (20.0)	
IV	3 (7.1)	2 (5.7)	

ICU, intensive care unit.

Table 5 Cumulative percentage change in body weight, BWL, and BMI

Variable	1 month after discharge		3 months after discharge		6 months after discharge	
	Intervention (n=33)	Control (n=31)	Intervention (n=33)	Control (n=31)	Intervention (n=33)	Control (n=31)
BWL	–3.16	–4.09	–5.46	–7.35	–6.01	–7.98
%BWL	4.52	5.92	7.77	10.63	8.52	11.52
<5%	19 (57.5%)	16 (51.6%)	9 (27.3%)	5 (16.1%)	5 (15.2%)	3 (9.7%)
5–10%	12 (36.4%)	11 (35.5%)	13 (39.4%)	11 (35.5%)	16 (48.5%)	9 (29%)
>10%	2 (6.1%)	4 (12.9%)	11 (33.3%)	15 (48.4%)	12 (36.3%)	19 (61.3%)
BMI change	–0.31	–1.44	–1.79	–2.57	–1.97	–2.80

BWL, body weight loss; BMI, body mass index.

respectively, at 3 and 6 months. The study by Froghi *et al.* (27), which investigated the value of 6 weeks enteral feeding following resection of an upper gastrointestinal malignancy, showed that the mean differences of BWL were 1.5 and 1.3 kg between the intervention group and control group at 12 and 24 weeks, respectively. Although these differences were obvious, there were not statistically significant. On the contrary, another study found that the BWL was significantly different at post-discharge 30 days in patients receiving an enhanced nutritional support pathway

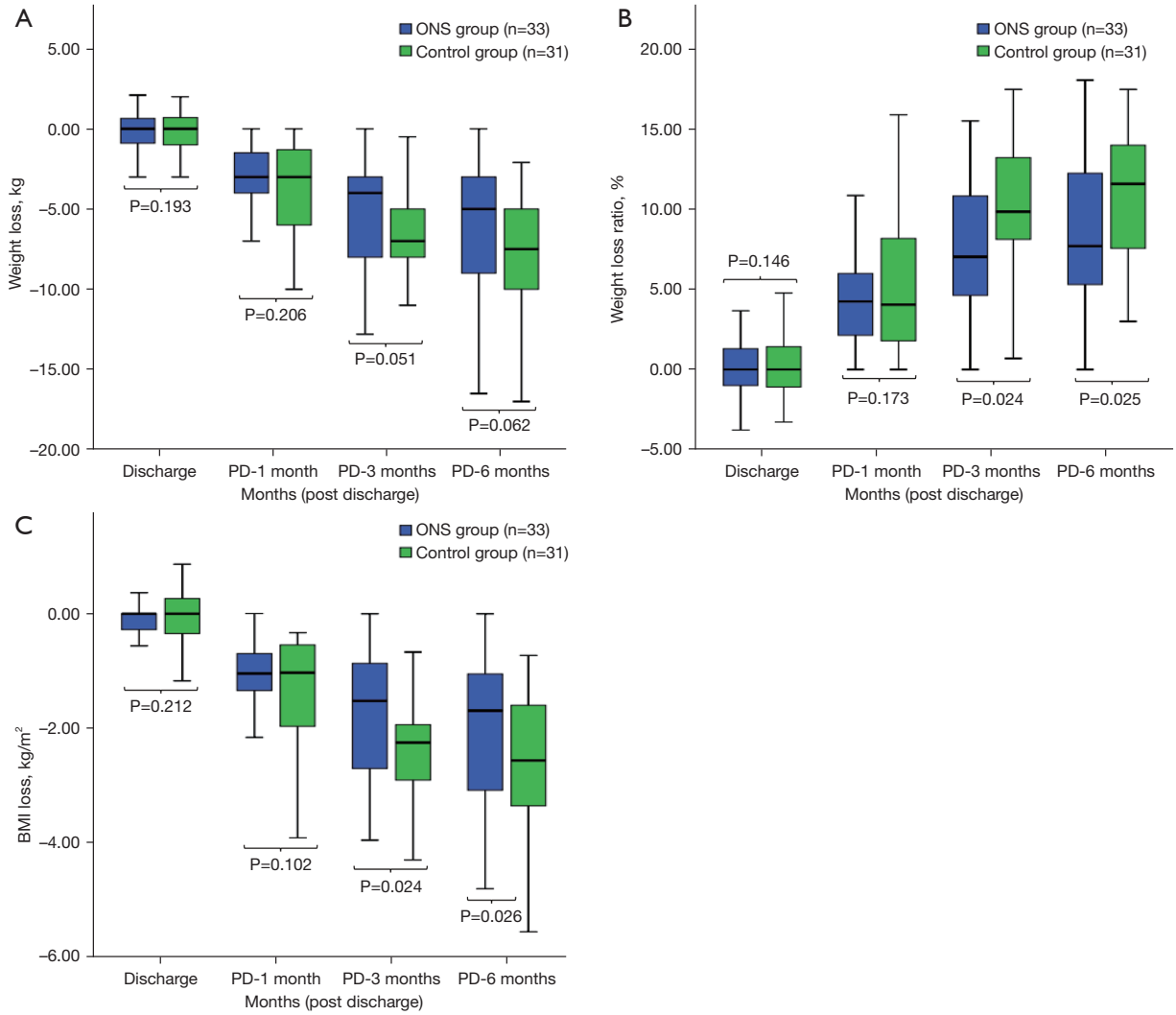

Figure 2 The changes of body weight and BMI according to the visit period. Body weight loss (A), %BWL (B) and BMI change (C) between the patient's presurgical body weight and that at discharge, 1, 3, and 6 months after discharge. PD, post discharge; BMI, body mass index.

Table 6 Main reported reasons for low compliance

Reasons for low compliance	Compliant patients (n=33) (%)	Non-compliant patients (n=8) (%)	P value
Flatulence	5 (15.2)	5 (62.5)	0.013
Diarrhea	4 (12.1)	6 (75.0)	0.001
Bellyache or stomach pain	4 (21.2)	3 (37.5)	0.378
Nausea or vomiting	3 (18.1)	2 (25.0)	0.642
Flavor dislike	5 (15.2)	3 (37.5)	0.172
No need for supplements	3 (9.1)	2 (25.0)	0.246
Continuously satiety	7 (24.2)	5 (62.5)	0.084
Other reasons	5 (15.2)	2 (25.0)	0.584

Table 7 Nutrition-related adverse events between the two groups

Variable	Intervention group (n=42) (%)	Control group (n=35) (%)	P value
Any type of adverse events	21 (50.0)	15 (42.9)	0.647
Flatulence	10 (23.8)	6 (17.1)	0.577
Diarrhea	10 (23.8)	7 (20.0)	0.786
Dysphagia	7 (16.7)	5 (14.3)	1.000
Nausea or vomiting/reflux	3 (7.1)	4 (11.4)	0.695
Dumping syndrome	4 (9.5)	3 (8.6)	1.000
Bellyache or stomach pain	6 (14.3)	4 (11.4)	0.748
Anorexia	5 (11.9)	3 (8.6)	0.721
Elevated AST/ALT level	3 (7.1)	4 (11.4)	0.695
Constipation	3 (7.1)	2 (5.7)	1.000

compared with conventional nutritional support (P=0.007). Previous studies have reported that 2/3 of patients had lost more than 10% of their preoperative weight at 6 months of discharge (24). In this study, 12 (12/33, 36.3%) participants who received ONS and 19 (19/31, 61.3%) participants in the control group lost more than 10% of their preoperative body weight at 6 months after discharge. These data reveal that nutritional support may decrease weight loss to some extent in the postoperative period.

In this study, the %BWL from the preoperative body weight in the ONS group was significantly lower than that in control group at 3 and 6 months (P=0.024, P=0.025, respectively). In other words, our result implied that short-term intervention with ONS for 4 weeks from the early postoperative days contributes to suppression of BWL at 3–6 months after discharge. Similar results on %BWL have also shown that additional ONS could reduce the %BWL in upper gastrointestinal cancer patients (30,31). The mean rate of BWL was greatest at 1 month post discharge and lowest from 3 to 6 months (5.2±4.1, 0.9±2.9, respectively). These findings were also broadly similar in another cohort (32).

Compliance with ONS, resulting in an increased total energy intake for patients, has been linked to clinical benefits (22). The follow-up point of post-discharge was scheduled at 1 month to evaluate the discomfort symptoms for ONS before adjuvant chemoradiotherapy, which could influence ONS compliance. A systematic review of 46 studies which explored the compliance to oral nutritional supplements found that the overall mean compliance with ONS was 78% (37–100%) and 62% of studies compliance was ≥75% (22). The mean compliance rate was 80% in this trial. The most common symptom for patients in the interventional group were diarrhea, flatulence, and continuous satiety after taking oral supplements. However, Lidoriki *et al.* reported that the compliance rate of upper gastrointestinal cancer patients with ONS was 65%, which is lower compared to the compliance rate shown in our study (33). The probable reasons are the diversity of flavor, texture, and lack of supervision and guidance of the prescribed supplements (34). Good compliance is the basis for patients to achieve significant improvements in weight loss and energy intake compared with usual care. Close postoperative supervision and guidance is the key to maximizing the consumption of ONS.

The treatment process of EC patients is very protracted, and may take 6 months to a year. Radical esophagectomy, often combined with preoperative or post-discharge chemotherapy and radiotherapy, has been shown to negatively impact many aspects of patient health-related quality of life (HRQOL) (35). On the contrary, treatment needs to simultaneously improve the nutritional status and physical fitness of cancer patients. The HRQOL is increasingly being viewed as an essential cancer care outcome (36). Thus, it is crucial to seek methods to improve the QoL in patients with EC. A study of HPN in advanced cancer patients showed that HPN is associated with an improvement in QoL (37). The QoL at 12 weeks was significantly better in the patients with parenteral nutrition supplementation (26). In this study, a significant improvement of QoL was observed at 1 month in the

Table 8 Quality of life score between the two groups at 5 points

Questionnaire Scales and Items	Pre-operation			Post discharge			1 month			3 months			6 months		
	ONS (n=33)	Control (n=31)	P value	ONS (n=33)	Control (n=31)	P value	ONS (n=33)	Control (n=31)	P value	ONS (n=33)	Control (n=31)	P value	ONS (n=33)	Control (n=31)	P value
Physical function	97.2±5.0	94.4±9.4	0.145	86.1±17.0	79.8±18.0	0.157	87.5±12.8	77.8±17.2	0.014	91.3±11.8	86.9±12.8	0.156	93.1±15.2	91.6±10.5	0.646
Role function	98.9±4.0	97.8±5.7	0.356	80.3±18.8	75.3±25.0	0.365	82.6±16.7	73.1±17.6	0.030	88.7±14.1	83.8±14.9	0.180	94.6±9.4	91.3±12.1	0.219
Emotional function	88.6±21.4	91.3±12.4	0.536	87.1±15.0	84.7±17.9	0.555	88.1±16.4	82.0±15.8	0.133	89.6±15.6	84.1±17.1	0.183	95.8±9.1	91.1±12.3	0.095
Cognitive function	95.5±8.6	97.3±7.6	0.364	81.8±18.3	74.2±20.6	0.122	95.9±8.4	91.4±12.8	0.100	96.9±6.5	91.4±12.8	0.915	99.5±2.9	98.9±4.2	0.525
Social function	91.9±12.6	88.7±16.3	0.380	80.8±19.1	75.3±20.1	0.264	85.9±15.7	81.7±15.0	0.429	94.4±9.0	92.4±11.8	0.429	93.9±9.1	89.8±13.4	0.156
Global quality of life	81.6±14.2	78.3±18.8	0.431	66.7±16.5	59.7±23.8	0.180	68.9±11.8	61.3±15.7	0.031	71.5±13.7	65.9±14.5	0.116	76.5±10.5	71.8±14.1	0.131
Fatigue	10.8±10.9	15.4±20.2	0.264	24.6±17.5	29.4±20.8	0.320	23.6±14.9	35.8±20.4	0.008	19.5±13.3	25.4±14.7	0.096	15.5±14.9	19.4±16.2	0.325
Nausea and vomiting	3.0±7.7	4.8±18.3	0.606	1.0±4.0	1.1±4.2	0.950	13.5±11.5	13.1±12.5	0.899	16.2±16.3	14.2±13.5	0.595	7.6±8.3	9.1±12.7	0.565
Pain	6.2±9.5	8.9±11.9	0.314	12.6±14.5	17.7±17.2	0.201	15.7±11.0	20.6±13.4	0.110	6.7±11.8	9.1±12.8	0.438	3.2±5.4	5.0±7.5	0.267
Dyspnea	1.0±5.8	4.3±11.4	0.155	18.2±23.7	21.5±23.6	0.550	18.2±23.7	23.7±21.4	0.337	10.8±13.7	16.5±15.4	0.122	8.1±12.5	12.1±15.5	0.251
Sleep disturbance	10.7±21.8	4.0±13.8	0.150	25.3±27.6	24.7±25.8	0.938	22.2±24.2	27.2±27.5	0.441	11.4±16.3	19.7±25.0	0.126	7.1±24.7	5.4±12.5	0.732
Appetite loss	7.5±20.6	6.1±13.1	0.733	11.1±18.0	10.8±18.0	0.937	19.2±26.4	23.7±23.1	0.475	14.1±26.4	19.4±24.0	0.412	10.8±17.0	15.4±19.8	0.318
Constipation	5.1±12.3	10.8±15.8	0.114	2.6±9.1	7.2±19.5	0.210	5.1±12.3	4.5±14	0.852	14.1±26.4	19.4±24.0	0.412	10.8±17.0	15.4±19.8	0.318
Diarrhea	11.1±58.1	8.6±21.0	0.821	9.1±15.1	12.9±16.5	8	12.1±18.3	10.8±15.8	0.751	14.1±22.1	18.3±16.9	0.405	12.5±18.5	17.2±20.9	0.347
Financial difficulties	9.1±17.2	7.5±14.2	0.694	13.1±23.5	19.4±24.0	0.299	9.1±15.1	12.9±18.6	0.370	11.1±15.1	15.1±20.8	0.441	5.1±13.9	7.9±13.5	0.412

ONS, oral nutrition supplement.

ONS group compared with the control group, which was consist with another trial (38). Klevebro and Froghi *et al.* found no evidence of improving QoL with postoperative enteral nutrition after esophagectomy combined with jejunostomy at 6 months (27,39). Our current findings also confirmed previous research. Nevertheless, we must highlight that the QoL scores of the present participants after esophagectomy were significantly higher than those reported in other studies of QoL at 6 months (9,28). An explanation might be that ONS played an important role, but not the only one.

To our knowledge, enteral nutrition and parenteral nutrition may produce many complications such as infection, thrombus, detachment, blocking, and so on, which deteriorate the QOL to a certain extent (40). As the key component of enhanced recovery protocols, early oral feeding is increasingly becoming the standard of care for gastrointestinal surgery (41). Although, oral intake is easily affected by diversity of flavor and texture of food (22). An early postoperative oral diet improves recovery of peristalsis, protects gut mucosal barrier function, and strengthens the immune response (9). All participants in our study could be satisfied with the criterion of early oral feeding without placing of a nasogastric tube and naso-jejunal feeding tube. Thus, on the basis of early oral feeding, we initiated this study to explore the effect of ONS on patients following esophagectomy. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend nutritional counseling and the use of ONS as first-line nutritional therapy (42).

Our study had some limitations. Firstly, it was a single center study and only enrolled patients contended to early oral feeding, so the diversities of nutritional management programs between different medical institutions may limit the generalizability and applicability of our findings. Secondly, a detailed survey of individual patients on their dietary caloric intake was not calculated after discharge. Therefore, it is unclear whether the total dietary caloric intake or composition was differentiated between the two groups. We did not have enough evidence to predict the mechanism of effects of ONS on %BWL. Third, partial patients with neoadjuvant therapy generally received preoperative nutritional support, which potentially influenced the outcome. Fourth, we only analyzed the BWL and BMI reduction in patients. Nevertheless, a number of cancer patients with normal or obese weight were affected by sarcopenia. Thus, the future trial should pay attention to the body composition of patients.

Conclusions

From the results we inferred that ONS has a positive effect on body weight and BMI loss and might improve QoL in patients following esophagectomy. In addition, we found no increased risk of adverse events when offering ONS. Thus, the nutritional support program was feasible and safe. Nevertheless, the finding may not be robust due to the small sample size. Future work should focus on the efficacy of individual nutritional therapy on the basis of a sufficient sample.

Acknowledgments

Funding: This study was supported by the China Cancer Foundation Beijing Hope Marathon Fund (N012063), Special Program for Basic Resource Survey of the Ministry of Science and Technology (2019FY101101) and Project of Incentive Program for Talent Introduction (N04204).

Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-5422

Trial Protocol: Available at https://dx.doi.org/10.21037/atm-21-5422

Data Sharing Statement: Available at https://dx.doi.org/10.21037/atm-21-5422

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-5422). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethical Review Committee of Cancer Hospital of Chinese Academy of Medical Sciences (21/058-2729). All patients were enrolled

after receiving detailed explanation of the study protocol and after they or their family members had provided written informed consent.

References

1. Liu J, Xie X, Zhou C, et al. Which factors are associated with actual 5-year survival of oesophageal squamous cell carcinoma? Eur J Cardiothorac Surg 2012;41:e7-11.
2. Krejs GJ. Gastric cancer: epidemiology and risk factors. Dig Dis 2010;28:600-3.
3. Wang J, Yang Y, Shaik MS. Prognostic significance of the number of lymph nodes dis-section in esophageal adenocarcinoma patients. Transl Cancer Res 2020;9:3406-15.
4. Biere SS, Maas KW, Cuesta MA, et al. Cervical or thoracic anastomosis after esophagectomy for cancer: a systematic review and meta-analysis. Dig Surg 2011;28:29-35.
5. Findlay JM, Gillies RS, Millo J, et al. Enhanced recovery for esophagectomy: a systematic review and evidence-based guidelines. Ann Surg 2014;259:413-31.
6. Brunelli A, Thomas C, Dinesh P, et al. Enhanced recovery pathway versus standard care in patients undergoing video-assisted thoracoscopic lobectomy. J Thorac Cardiovasc Surg 2017;154:2084-90.
7. Weimann A, Braga M, Carli F, et al. ESPEN guideline: Clinical nutrition in surgery. Clin Nutr 2017;36:623-50.
8. Shoar S, Naderan M, Mahmoodzadeh H, et al. Early Oral Feeding After Surgery for Upper Gastrointestinal Malignancies: A Prospective Cohort Study. Oman Med J 2016;31:182-7.
9. Sun HB, Li Y, Liu XB, et al. Early Oral Feeding Following McKeown Minimally Invasive Esophagectomy: An Open-label, Randomized, Controlled, Noninferiority Trial. Ann Surg 2018;267:435-42.
10. Berkelmans GHK, Fransen LFC, Dolmans-Zwartjes ACP, et al. Direct Oral Feeding Following Minimally Invasive Esophagectomy (NUTRIENT II trial): An International, Multicenter, Open-label Randomized Controlled Trial. Ann Surg 2020;271:41-7.
11. Berkelmans GH, Wilts BJ, Kouwenhoven EA, et al. Nutritional route in oesophageal resection trial II (NUTRIENT II): study protocol for a multicentre open-label randomised controlled trial. BMJ Open 2016;6:e011979.
12. Kingma BF, Steenhagen E, Ruurda JP, et al. Nutritional aspects of enhanced recovery after esophagectomy with gastric conduit reconstruction. J Surg Oncol 2017;116:623-9.
13. Deans DA, Tan BH, Wigmore SJ, et al. The influence of systemic inflammation, dietary intake and stage of disease on rate of weight loss in patients with gastro-oesophageal cancer. Br J Cancer 2009;100:63-9.
14. Kenny C, Regan J, Balding L, et al. Dysphagia Prevalence and Predictors in Cancers Outside the Head, Neck, and Upper Gastrointestinal Tract. J Pain Symptom Manage 2019;58:949-958.e2.
15. Ginex P, Thom B, Jingeleski M, et al. Patterns of symptoms following surgery for esophageal cancer. Oncol Nurs Forum 2013;40:E101-7.
16. Martin L, Lagergren J, Lindblad M, et al. Malnutrition after oesophageal cancer surgery in Sweden. Br J Surg 2007;94:1496-500.
17. Lee JLC, Leong LP, Lim SL. Nutrition intervention approaches to reduce malnutrition in oncology patients: a systematic review. Support Care Cancer 2016;24:469-80.
18. Ravasco P, Monteiro-Grillo I, Camilo M. Individualized nutrition intervention is of major benefit to colorectal cancer patients: long-term follow-up of a randomized controlled trial of nutritional therapy. Am J Clin Nutr 2012;96:1346-53.
19. Baldwin C, Spiro A, Ahern R, et al. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. J Natl Cancer Inst 2012;104:371-85.
20. Enriquez-Fernández BE, Nejatinamini S, Campbell SM, et al. Sensory preferences of supplemented food products among cancer patients: a systematic review. Support Care Cancer 2019;27:333-49.
21. de Luis DA, Izaola O, Lopez JJ, et al. Oral Nutritional Supplements and Taste Adherence in Malnourished Adults Inpatients, Effect on Adhesion during Hospital Stance. Ann Nutr Metab 2015;67:205-9.
22. Hubbard GP, Elia M, Holdoway A, et al. A systematic review of compliance to oral nutritional supplements. Clin Nutr 2012;31:293-312.
23. Martin L, Senesse P, Gioulbasanis I, et al. Diagnostic

criteria for the classification of cancer-associated weight loss. J Clin Oncol 2015;33:90-9.
24. Baker M, Halliday V, Williams RN, et al. A systematic review of the nutritional consequences of esophagectomy. Clin Nutr 2016;35:987-94.
25. Liu K, Ji S, Xu Y, et al. Safety, feasibility, and effect of an enhanced nutritional support pathway including extended preoperative and home enteral nutrition in patients undergoing enhanced recovery after esophagectomy: a pilot randomized clinical trial. Dis Esophagus 2020;33:doz030.
26. Obling SR, Wilson BV, Pfeiffer P, et al. Home parenteral nutrition increases fat free mass in patients with incurable gastrointestinal cancer. Results of a randomized controlled trial. Clin Nutr 2019;38:182-90.
27. Froghi F, Sanders G, Berrisford R, et al. A randomised trial of post-discharge enteral feeding following surgical resection of an upper gastrointestinal malignancy. Clin Nutr 2017;36:1516-9.
28. Demas GE, Drazen DL, Nelson RJ. Reductions in total body fat decrease humoral immunity. Proc Biol Sci 2003;270:905-11.
29. Bowrey DJ, Baker M, Halliday V, et al. A randomised controlled trial of six weeks of home enteral nutrition versus standard care after oesophagectomy or total gastrectomy for cancer: report on a pilot and feasibility study. Trials 2015;16:531.
30. Imamura H, Nishikawa K, Kishi K, et al. Effects of an Oral Elemental Nutritional Supplement on Post-gastrectomy Body Weight Loss in Gastric Cancer Patients: A Randomized Controlled Clinical Trial. Ann Surg Oncol 2016;23:2928-35.
31. Hatao F, Chen KY, Wu JM, et al. Randomized controlled clinical trial assessing the effects of oral nutritional supplements in postoperative gastric cancer patients. Langenbecks Arch Surg 2017;402:203-11.
32. Donohoe CL, Healy LA, Fanning M, et al. Impact of supplemental home enteral feeding postesophagectomy on nutrition, body composition, quality of life, and patient satisfaction. Dis Esophagus 2017;30:1-9.
33. Lidoriki I, Schizas D, Mylonas KS, et al. Oral Nutritional Supplementation Following Upper Gastrointestinal Cancer Surgery: A Prospective Analysis Exploring Potential Barriers to Compliance. J Am Coll Nutr 2020;39:650-6.
34. Hogan SE, Solomon MJ, Carey SK. Exploring reasons behind patient compliance with nutrition supplements before pelvic exenteration surgery. Support Care Cancer 2019;27:1853-60.
35. Jacobs M, Macefield RC, Elbers RG, et al. Meta-analysis shows clinically relevant and long-lasting deterioration in health-related quality of life after esophageal cancer surgery. Qual Life Res 2014;23:1097-115.
36. Gannon JA, Guinan EM, Doyle SL, et al. Reduced fitness and physical functioning are long-term sequelae after curative treatment for esophageal cancer: a matched control study. Dis Esophagus 2017;30:1-7.
37. Vashi PG, Dahlk S, Popiel B, et al. A longitudinal study investigating quality of life and nutritional outcomes in advanced cancer patients receiving home parenteral nutrition. BMC Cancer 2014;14:593.
38. Senkal M, Zumtobel V, Bauer KH, et al. Outcome and cost-effectiveness of perioperative enteral immunonutrition in patients undergoing elective upper gastrointestinal tract surgery: a prospective randomized study. Arch Surg 1999;134:1309-16.
39. Klevebro F, Johar A, Lagergren J, et al. Outcomes of nutritional jejunostomy in the curative treatment of esophageal cancer. Dis Esophagus 2019;32:doy113.
40. Braga M, Gianotti L, Gentilini O, et al. Early postoperative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition. Crit Care Med 2001;29:242-8
41. Minig L, Biffi R, Zanagnolo V, et al. Reduction of postoperative complication rate with the use of early oral feeding in gynecologic oncologic patients undergoing a major surgery: a randomized controlled trial. Ann Surg Oncol 2009;16:3101-10.
42. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr 2017;36:11-48.

(English Language Editor: J. Jones)

Cite this article as: Xie H, Chen X, Xu L, Zhang R, Kang X, Wei X, Yang Y, Li Y. A randomized controlled trial of oral nutritional supplementation versus standard diet following McKeown minimally invasive esophagectomy in patients with esophageal malignancy: a pilot study. Ann Transl Med 2021;9(22):1674. doi: 10.21037/atm-21-5422

