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Early oral feeding following McKeown minimally invasive esophagectomy: an open-label, randomized, controlled, non-inferiority trial

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Abstract

Objective—Our objective was to evaluate the impact of early oral feeding (EOF) on postoperative cardiac, respiratory and gastrointestinal (CRG) complications after McKeown minimally invasive esophagectomy (MIE) for esophageal cancer.

Summary Background Data—Nil-by-mouth with enteral tube feeding is routinely practiced after esophagectomy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicate no potential relevant conflicts of interest.

Methods—Patients were randomly allocated to receive oral feeding on the first postoperative day (EOF group) or late oral feeding (LOF group) 7 days after surgery. The primary endpoint was the occurrence of postoperative CRG complications, and the secondary outcomes included bowel function recovery and short-term quality of life (QOL).

Results—Between February 2014 and October 2015, 280 patients were enrolled in this study. There were 140 patients in the EOF group and 140 patients in the LOF group. EOF was non-inferior to LOF for CRG complications (25.0% in the EOF group versus 27.9% in the LOF group; 95% confidence interval: −13.2% – 7.4%). Compared with the LOF group, the EOF group showed significantly shorter time to first flatus (median of 2 days versus 3 days, $P = 0.001$) and bowel movement (median of 3 days versus 4 days, $P < 0.001$). Two weeks after the operation, patients in the EOF group reported higher global QOL and function scores and lower symptom scores than patients in the LOF group.

Conclusions—EOF in patients after McKeown MIE is non-inferior to the standard of care with regard to postoperative CRG complications. In addition, patients in the EOF group had a quicker recovery of bowel function and improved short-term QOL.

INTRODUCTION

Esophageal cancer is among the fastest growing human cancers, and causes more than 400,000 deaths worldwide annually.¹ Despite advances in diagnosis and treatment, esophageal cancer remains a highly lethal malignancy. Currently, esophagectomy is the standard treatment for resectable esophageal cancer. However, esophagectomy is associated with high morbidity, a relatively long hospital stay and slow recovery of baseline activity levels.² Although minimally invasive esophagectomy (MIE) has emerged as an alternative to traditional open approaches, postoperative care does not differ between MIE and open resection.^{3,4} In particular, most surgeons still adhere to ‘nil by mouth’ during the early postoperative period after esophagectomy and prefer enteral tube feedings distal to the new anastomosis for enteral nutritional support. Although enteral catheter feeding has been shown to be beneficial in patients with esophagectomy,⁵ this preference is mainly based on traditional but unfounded reluctance to allow food by mouth.

The results of our prior retrospective study showed that early postoperative gastric emptying of liquid food after McKeown MIE is significantly faster than preoperative gastric emptying and that early oral feeding (EOF) is feasible.⁶ To further evaluate the safety and advantages of EOF in patients with esophageal cancer undergoing McKeown MIE, we completed a prospective randomized controlled trial with the clinical hypothesis that EOF is non-inferior to the standard of care (nil by mouth until 7 days after surgery) with respect to postoperative cardiac, respiratory and gastrointestinal (CRG) complications; moreover, we hypothesized that EOF facilitates recovery of intestinal function and improves short-term quality of life (QOL).

PATIENTS AND METHODS

Study Design

This was a prospective, single-center, randomized, non-inferiority trial conducted at The Thoracic Surgery Unit of The Affiliated Cancer Hospital of Zhengzhou University. No changes were made to the methods, type of randomization or eligibility criteria after trial commencement. Participants were informed that their participation was voluntary and that they could withdraw their consent to participate at any time during the study without any consequences for their care. All patients were informed verbally and in writing, and written consent was obtained before entering the study. The study design, which was planned according to the CONSORT guidelines, was approved by the Affiliated Cancer Hospital of Zhengzhou University Ethics Committee (2014xjs4) and was conducted in accordance with the Declaration of Helsinki. The study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (registration number: NCT01998230).

Participants

All consecutive patients aged 18 years undergoing McKeown MIE with cervical hand-sewn anastomosis for esophageal cancer were eligible. Preoperative exclusion criteria were (i) age 80 years; (ii) inability to perform McKeown MIE due to tumor extension; (iii) severe preoperative comorbidities and inability to undergo MIE (FEV1 < 50% predicted, EF < 50% and organ failure); (iv) obvious hepatocirrhosis; (v) diabetes with organ injury; and (vi) lack of written informed consent to participate. Postoperative exclusion criteria were (i) exploratory surgery; (ii) recovery in the intensive care unit (ICU) for more than 24 hours; and (iii) bilateral recurrent laryngeal nerve (RLN) injury.

Standard preoperative staging investigations included endoscopic ultrasonography, computed tomography scans of the brain, chest and abdomen and bone scintigraphy. Positron emission tomography with fluorodeoxyglucose was used when distant metastasis was suspected. The patients were staged using the 7th edition of the tumor, node, metastasis (TNM) classification of malignant tumors.⁷ Comorbidities were scored according to Charlson's comorbidity index.⁸ Nutritional risk screening (NRS) using NRS 2002 was applied for all patients with esophageal cancer. Patients with an NRS score of 3 points were included in the nutrition support program. Enteral nutrition was administered from the early preoperative stage (5–7 days) to support treatment under the guidance of dietitians. Smoking cessation for more than 2 weeks before surgery was necessary for all patients. For patients with diabetes, fasting blood glucose was controlled below 8.3 mmol/L before surgery. All patients were discussed preoperatively by a multidisciplinary expert panel to delineate the best treatment approach.

Operation

All patients underwent McKeown MIE with two-field or three-field lymph node dissection, as described previously⁶ (see Figures, Supplemental Figure Content 1, which demonstrates the surgical procedures of McKeown MIE), and all operations were performed by one surgical team led by one author (LY). Initially, each patient was placed in the left lateral decubitus position. Four ports were placed in the chest, and the thoracic esophagus was

mobilized, after which the lymph nodes were harvested. Following the thoracic procedure, the patient was transferred to the supine position, and five ports were placed in the abdominal wall. The stomach was then mobilized, with careful preservation of the right gastroepiploic pedicle. Linear cutting staplers (EC60, Ethicon, USA) were then used to make a 4-cm-wide gastric conduit and no gastric emptying procedure was performed. Finally, a hand-sewn, three-layer embedded cervical esophagogastric anastomosis was constructed.⁹ Briefly, the mucosal layer and muscular layer were sutured separately. Following the creation of a two-layer anastomosis, the redundant gastric tube was excised two cm above the anastomotic site, and the remnant gastric tube was embedded into the gastric cavity. A row of interrupted sutures was then placed between the muscular layer of the gastric tube and the esophagus.

Patients were extubated and transferred directly to the surgical ward following stabilization in the recovery room. A planned one day stay in the ICU was needed for patients who were 75 years of age, who had a history of coronary artery disease, who required mechanical ventilation and/or who had an operation time greater than 5 hours.

Intervention

Both groups were treated similarly in the perioperative period, and no nasogastric tube was placed before or during the operation in either group. All patients underwent endoscopic examination at bedside on postoperative day (POD) 1 to determine vocal cord function. Upper gastrointestinal tract radiography was performed only when leakage, delayed gastric emptying, diaphragmatic hernia, or intestinal obstruction was suspected. When leakage occurred, patients underwent nasogastric decompression and cervical or mediastinal drainage. The discharge criteria were the presence of normal vital signs, ability to tolerate a soft diet, no signs of a postoperative complication that needed to be treated at the hospital, ability to ambulate without assistance, tolerable pain on oral analgesia, and willingness to go home.

Active Group—In the EOF group, patients were encouraged to consume food on the morning of the first POD according to the following protocol. Before oral feeding, EOF patients were allowed to have sips of thin liquids while being observed for any symptoms of aspiration, including coughing, throat clearing, and voice changes. If no signs of aspiration were observed by the trained clinician, oral feeding was allowed. Dieticians provided nutrition education for all patients in the EOF group, and strict aspiration precautions were stressed. At POD 1, liquid foods such as milk, porridge and juice were administered. At POD 2, semi-liquid foods and soft solid foods such as cakes, noodles, rice, eggs and steamed bread were allowed. We encouraged patients to chew carefully and completely when eating soft solid food. Dieticians calculated caloric requirements using the Harris-Benedict formula for postoperative energy requirements and measured patients' kilocalorie intake per day. Parenteral nutrition via a central line was also administered and comprised fat emulsion, amino acids and glucose to provide a total of 1000–1500 kilocalories (kcal), 800–1000 kcal, and 500–800 kcal on POD 1, POD 2 and POD 3, respectively. In case of aspiration, severe distension, or signs of leakage, oral intake was halted. At POD 4, parenteral nutrition was stopped unless the patient could not consume food orally because of complications.

Control Group—In the LOF group, nasogastric and nasoenteral feeding tubes were placed with the help of interventional radiology on POD 1. The patients received nutrition via a nasoenteral feeding tube at 40 mL/h on POD 1, and the rate was increased by 40 mL/h each day, if tolerated, up to 120 mL/h. Parenteral nutrition was also used from POD 1 to POD 3 in the LOF group. On POD 7, the nasogastric tube was removed, and the patients were allowed the same food as in the EOF group according to the dieticians' guidance. Enteral infusion was halted and the nasoenteral feeding tube was removed if the patients could tolerate soft food.

Primary Endpoints

The primary endpoint was to assess postoperative CRG complications during hospital stay in both groups. The definition of each complication is listed in Supplemental Table Content 2. Complications were also graded based on the Clavien-Dindo classification.¹⁰ For patients with two or more complications only the highest grade was reported, while death (Grade V) and blood transfusion (Grade II) were reported separately. We also recorded other data including the need for ICU re-admission, the need for nasogastric tube insertion, and re-admission within 30 days.

Secondary Endpoints

The secondary endpoints were to evaluate bowel function recovery (measured as the time to first flatus and to first bowel movement) and patients' short-term QOL in both groups. The European Organization for Research and Treatment of Cancer (EORTC) questionnaires C30 and OES18 were used to assess QOL at baseline (1 week before surgery) and 2 weeks, 4 weeks, 8 weeks, 12 weeks and 24 weeks after surgery. Baseline data were collected in hospital, and follow-up assessments were arranged by telephone and performed by mail, with one telephone reminder if required. In addition, we analyzed the length of postoperative stay (days) and kilocalories intake.

Sample Size

The sample size was calculated based on the primary outcome. We set the non-inferiority margin at 13%, meaning that when the upper limit of the 95% confidence interval (CI) for the estimated difference in the postoperative CRG complication rate between the EOF group and the control group exceeded 13%, the EOF group would be inferior to the control group. We assumed a postoperative CRG complication rate of 23%, as estimated in a previous study,⁶ and a single-sided α risk of 0.05. With two groups of 130 patients each, the trial had 80% power with a prespecified non-inferiority margin of 13% to assess the non-inferiority of EOF. Considering the drop-out rate, a total of 280 patients was the planned enrollment for this study.

Randomization

Computerized randomization lists were created, and the results were placed in sealed opaque envelopes by individuals not involved in the trial. If the inclusion criteria were fulfilled at POD 1, the patients were randomly allocated (1:1) to the EOF group or LOF group. The intervention in this study was not blind.

Statistical Analysis

Data are reported as medians and interquartile ranges for continuous variables and as absolute number and percentage for categorical variables. QOL data are presented as means and standard deviations. The Chi-square test and Fisher's exact test were used for categorical data. Comparisons between the two groups were performed using the t-test for independent samples in cases of normal data distribution and the Mann-Whitney U test in cases of non-normal data distribution. We assessed the study outcomes by intention-to-treat (ITT) analysis and the ITT set included all patients randomized.

RESULTS

From February 2014 to October 2015, a total of 396 patients were assessed for eligibility, and 116 patients were excluded for the following reasons: not a candidate for McKeown MIE (n = 104); had severe comorbidity (n = 3); had advanced age (n = 2); refused to participate (n = 2); underwent exploratory surgery (n = 1); had bilateral RLN injury (n = 2); or remained in the ICU for more than 24 hours (n = 2, one required mechanical ventilation for more than 24 hours, and one showed clinical evidence of cardiac failure). A total of 24 patients had a planned one-day stay in the ICU after surgery. Thus, 280 patients were enrolled and allocated to the EOF group (n = 140) and LOF group (n = 140). In the EOF group, all patients but one who developed acute respiratory distress syndrome (ARDS) received oral intake as scheduled. However, 9 patients did not complete the oral intake program postoperatively due to complications, which included anastomotic leak (n = 4), aspiration (n = 2), delayed gastric emptying (n = 1), pneumothorax (n = 1) and chylothorax (n = 1). A total of 10 patients had symptoms of aspiration; 8 of these patients could still tolerate oral intake after guidance on dietary changes and chin-down maneuver, and 2 patients could not tolerate oral feeding and discontinued oral intake. In the LOF group, 137 patients received the conventional nutritional program except three patients in whom a feeding tube could not be successfully placed. A flow chart of the study is presented in Figure 1. The demographic, clinical, operative and pathological characteristics of the two groups are summarized in Table 1.

Primary Endpoints

The results for the primary outcome and the additional postoperative complications are outlined in Table 2. No deaths occurred in either of the two groups in the hospital or within 30 days after esophagectomy. EOF was non-inferior to traditional care (LOF) in terms of CRG complications (30.0% in the EOF group versus 32.9% in the LOF group, or a difference of -2.9%; 95% CI -13.8% - 8.0%) based on ITT analysis. No notable differences were observed in the rate of other complications (15.7% in the EOF group versus 18.6% in the LOF group, or a difference of -2.9%; 95% CI -11.7% - 5.9%) or in the rate of any complications (34.3% in the EOF group versus 38.6% in the LOF group, or a difference of -4.3%; 95% CI -15.6% - 7.0%). The rates of anastomotic leak in the EOF group and LOF group were 3.6% (5/140) and 4.3% (6/140), respectively, representing a difference of -0.7% (95% CI -3.8% - 2.4%). The rates of unilateral RLN injury in the EOF group and the LOF group were 10.0% (14/140) and 10.7% (15/140), respectively, representing a difference of -0.7% (95% CI -7.8% - 6.4%). The most common complication was pneumonia, which

occurred in 10.7% (15/140) of EOF patients and in 12.1% (17/140) of LOF patients, representing a difference of -1.4% (95% CI $-15.6\% - 7.0\%$). Additionally, no significant differences were found in the Clavien-Dindo grade of different types of complications between the two groups.

Five (3.6%) patients in the EOF group and 9 (6.4%) patients in the LOF group required re-admission to the ICU (difference of -2.8% ; 95% CI $-7.9\% - 2.3\%$). Eight (5.7%) patients in the EOF group and 11 (7.9%) patients in the LOF group required therapeutic decompression nasogastric tubes (difference of -2.2% ; 95% CI $-8.1\% - 3.7\%$). Two (1.4%) patients (one with pneumonia, one with wound infection) in the EOF group and 1 (0.7%) patient (with pneumonia) in the LOF group underwent unscheduled re-admission within 30 days. No patients were subsequently diagnosed with anastomotic leakage during the follow-up period.

Secondary Endpoints

Bowel Function and Length of Postoperative Hospital Stay—The results are summarized in Table 3. Compared to the LOF group, the EOF group presented a significant shorter time to first flatus ($P = 0.001$) and to first bowel movement ($P < 0.001$). Compared to the LOF group, the EOF group presented a significantly shorter length of postoperative stay (7 (7–8) days versus 10 (9–12) days, respectively, $P < 0.001$).

Dietary Outcome—The median amounts of oral kcal intake in the EOF group at POD 1, POD 3 and POD 5 were 80 (60–110) kcal, 750 (634–860) kcal, and 1260 (1120–1650) kcal, respectively. At POD 5, the median oral intake was 70% (62.2%–91.7%) of target kilocalories. When discharged home, the median oral intake was 1566 (1365–1682) kcal, which was 87% (75.8%–93.4%) of target kilocalories. Eight (5.7%) patients in the EOF group still required parenteral nutrition at POD 4, including 1 patient with ARDS, 2 patients with aspiration, 3 patients with anastomotic leak, 1 patient with delayed gastric emptying and 1 patient with chylothorax. Median weight loss 1 month postoperatively was 1.8 (1.3–3.8) kg in the EOF group and 1.7 (1.2–3.9) kg in the LOF group ($P = 0.327$). No patients in the EOF group needed to be admitted for nutritional support during the 24 weeks of follow-up.

QOL Assessment—No significant differences in baseline QOL scores were observed between the two groups. Two patients in the EOF group and three patients in the LOF group died during the 24 weeks of follow-up. Two weeks after the operation, global QOL ($P = 0.002$), physical function ($P = 0.017$), emotional function ($P < 0.001$), and social function ($P < 0.001$) were significantly higher in patients in the EOF group than in patients in the LOF group. Two weeks after the operation, patients in the LOF group reported statistically significantly more problems with fatigue ($P < 0.001$), nausea and vomiting ($P < 0.001$), pain ($P < 0.001$), appetite loss ($P = 0.003$), diarrhea ($P < 0.001$), dysphagia ($P < 0.001$), eating difficulties ($P = 0.002$) and trouble swallowing saliva ($P < 0.001$) than patients in the EOF group. Four weeks after the operation, patients in the EOF group reported higher global QOL ($P < 0.001$) and fewer symptoms of nausea and vomiting ($P = 0.002$), and diarrhea ($P = 0.037$) (Table 4).

DISCUSSION

Despite recent reviews indicating that EOF is a safe strategy without any significant increase in complications in patients undergoing colonic^{11, 12} and gastric surgery,¹³ many surgeons remain reluctant to administer EOF to patients after esophagectomy. The main reason for supporting traditional oral intake restriction after esophagectomy is the concern for anastomosis leakage. However, experimental studies in a rat model have shown that EOF after upper gastrointestinal surgery facilitates anastomotic healing.¹⁴ In addition, an early postoperative oral diet improves recovery of peristalsis, protects gut mucosal barrier function, and strengthens the immune response.¹⁵ Another concern for early eating after esophagectomy, especially after McKeown with cervical anastomosis, is that subtle or overt vocal cord injury may contribute to aspiration and thus aspiration pneumonia.

In the present study, we aimed to demonstrate the safety and advantages of EOF after esophagectomy as reported previously for other types of abdominal surgery. The current study is the largest randomized controlled clinical trial to date evaluating the safety and advantages of EOF after McKeown MIE. Our study showed that allowing patients to slowly and carefully consume liquid and food immediately after McKeown MIE for esophageal cancer was non-inferior to the standard regimen of nil by mouth and enteral feeding for 6 days in terms of CRG complications. No surgical or anastomosis site-associated adverse events were observed. Therefore, it might not be justified to practice oral intake restriction for fear of anastomosis dehiscence and pneumonia. The results of our study are consistent with the results of a prior study investigating whether allowing regular food immediately after major upper gastrointestinal (GI) surgery increased morbidity. The results of that study showed that allowing patients to eat regular food at will from the first day after major upper GI surgery did not increase morbidity compared with traditional nil by mouth and enteral feeding.¹⁶ However, only 8 patients with esophagectomy were enrolled in this randomized study, including 2 transhiatal esophagectomies and 6 transthoracic esophagectomies; subgroup analysis was not performed. Furthermore, the kcal intake in the EOF group was not calculated.

In the current study, EOF improved the recovery of gut function, as indicated by the times to first flatus and bowel movement, which were significantly shorter for those who were allowed to eat at POD 1. Although earlier bowel function recovery may not change clinical care for patients with esophagectomy, we believe that eating food, through the activation of normal digestive reflexes, has an important impact on gut recovery, which in turn is central in overall recovery after esophagectomy. The length of postoperative stay was also significantly shorter in the EOF group compared with the LOF group. However, since being able to tolerate a soft diet was mandatory to meet the discharge criteria, a shorter postoperative stay might not be representative of faster recovery.

In our study, most patients (130/140, 92.9%) with McKeown MIE could tolerate the EOF regimen, with only ten patients in the EOF group unable to receive or needing to discontinue the EOF regimen. All ten patients recovered and were discharged home after treatment, with no severe adverse outcomes. Based on the postoperative calorie intake, we conclude that patients can tolerate EOF very well. The early resumption of oral nutrition might be

enhanced by adopting multiple practice changes (such as minimally invasive surgery, no nasogastric drainage, no enteral feeding tube and early mobilization) to reduce postoperative surgical stress. The findings indicate that patients can tolerate oral intake well and that early withdrawal of parenteral nutrition (at POD 4 in our study) is feasible and safe. We do not claim that allowing EOF confers nutritional benefits in the early postoperative period or that the selective use of nutritional support is never needed. However, our results indicate that allowing these patients to eat might be beneficial. A jejunostomy feeding tube remains indicated for the supplemental administration of nutrients when patients cannot receive sufficient oral nutrition after esophagectomy. However, jejunostomy is not considered the standard of care for patients with esophagectomy in China since resources for home care are lacking, and jejunostomy feeding can be associated with many minor complications (13%–38%), and occasionally severe complications (0%–3%) that require reoperation.¹⁷ For these reasons a nasoenteric tube is most commonly used for post-operative feeding in China. These findings suggest that further international multi-center studies investigating EOF and jejunostomy feeding should be considered in this nutritionally-compromised population.

Esophageal cancer surgery has a considerable detrimental effect on the QOL of patients in the short term.^{18, 19} Some studies have indicated that after an initial decline, QOL recovers to baseline levels within 1 to 3 years after surgery.^{18, 20} In accordance with previous studies^{18, 19} the results of our study showed that QOL declined markedly in all patients at 2 weeks post-surgery but gradually returned toward baseline within the first half year thereafter. It seems obvious that a patient with a nasoenteral tube and nasogastric tube in place for at least 6 days would have a decreased early QOL score. However, to determine which QOL items differed between the two groups and the duration of these differences, we chose QOL as one of the secondary endpoints. The results of our study indicate that compared with nil by mouth for 6 days, EOF after McKeown MIE was associated with improved short-term QOL. This is the first report regarding the impact of EOF in QOL for patients receiving McKeown MIE. The exact mechanism of the association of EOF and QOL remains to be elucidated, but some speculative mechanisms might have explanatory value. The absence of a nasogastric or enteral feeding tube and the lack of fasting may reduce patient discomfort.

Limitations

Our analysis has certain limitations, mainly because of its nature as a single-center study. Moreover, in this study, we only included patients with MIE with hand-sewn cervical anastomosis, and the rate of postoperative complications was relatively low in both groups. We did not investigate the feasibility of EOF in patients with other surgical procedures, such as open surgery, and with different anastomotic methods such as a stapled intrathoracic anastomosis. As the patients included in our study were relatively young, with few comorbidities and a low percentage of neoadjuvant therapy (31.1%, 87/280), further studies are needed to investigate the feasibility of EOF among patients in worse condition.

CONCLUSIONS

In selected cases, EOF after MIE is a safe and feasible strategy. An early recovery of intestinal function and an improvement of QOL are the main advantages of EOF versus LOF. Our data should be confirmed by further studies before EOF can be routinely advocated in clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Flowchart of the study.

Abbreviations: MIE = minimally invasive esophagectomy; RLN = recurrent laryngeal nerve;

ICU = intensive care unit; POD = postoperative day; QOL = quality of life

TABLE 1

Basic patient characteristics and clinical data

Characteristic	EOF Group (n = 140)	LOF Group (n = 140)	P
Age (years)	63 (58–68)	63 (58–69)	0.517
Sex			0.153
Male	92 (65.7%)	103 (73.6%)	
Female	48 (34.3%)	37 (26.4%)	
Location of tumor			0.197
Upper	25 (17.9%)	20 (14.3%)	
Middle	59 (42.1%)	76 (54.3%)	
Lower	54 (38.6%)	41 (29.3%)	
Multiple	2 (1.4%)	3 (2.1%)	
Neoadjuvant therapy (Yes/No)	38/102	49/91	0.155
Chemotherapy	36 (25.7%)	47 (33.6%)	0.150
Chemoradiotherapy	2 (1.4%)	2 (1.4%)	1.000
Charlson's comorbidity index	1 (0–2)	1 (0–2)	0.375
Preoperative albumin level (g/L)	43.4 (41.6–46.3)	43.1 (40.6–46.9)	0.232
BMI (kg/m ²)	23.4 (21.7–25.7)	23.6 (21.5–25.7)	0.682
Operation time (min)	180 (168–210)	182 (170–210)	0.166
Blood transfusion (Yes/No)	2/138	4/136	0.684
Lymphadenectomy			
3-Field	4	5	0.735
2-Field	136	135	
No. of harvested lymph nodes	26 (20–37)	24 (23–36)	0.130
Histology			
Squamous cell carcinoma	132	133	0.434
Adenocarcinoma	2	4	
Other	6	3	
Differentiation			0.426
Poor	33	42	
Moderate	56	55	
High	43	36	
Pathologic stage			0.800
0	10	10	
I	22	28	
II	66	60	
III	42	42	

Abbreviations: EOF = early oral feeding; LOF = late oral feeding; BMI = body mass index

TABLE 2

Perioperative outcomes in the two groups

Variable	ITT analysis		
	EOF Group (n = 140)	LOF Group (n = 140)	Difference (95% CI)
Cardiac Complications (total)	14 (10.0%)	17 (12.1%)	-2.1% (-9.4% - 5.2%)
Myocardial arrhythmia	13 (9.3%)	15 (10.7%)	-1.4% (-8.4% - 5.6%)
Heart failure	1 (0.7%)	2 (1.4%)	-0.7% (-3.1% - 1.7%)
Respiratory Complications (total)	31 (22.1%)	40 (28.6%)	-6.5% (-16.7% - 3.7%)
Pneumonia	15 (10.7%)	17 (12.1%)	-1.4% (-8.8% - 6.0%)
Respiratory failure	2 (1.4%)	4 (2.9%)	-1.5% (-4.9% - 1.9%)
ARDS	2 (1.4%)	3 (2.1%)	-0.7% (-3.8% - 2.4%)
Atelectasis	3 (2.1%)	5 (3.6%)	-1.5% (-5.4% - 2.4%)
Pneumothorax	4 (2.9%)	2 (1.4%)	1.5% (-1.9% - 4.9%)
Pleural effusions	3 (2.1%)	5 (3.6%)	-1.5% (-5.4% - 2.4%)
Mediastinitis	2 (1.4%)	4 (2.9%)	-1.5% (-4.9% - 1.9%)
Gastrointestinal complications (total)	6 (4.3%)	8 (5.7%)	-1.4% (-6.5% - 3.7%)
Anastomotic leak	5 (3.6%)	6 (4.3%)	-0.7% (-5.3% - 3.9%)
Intestinal obstruction	0	1 (0.7%)	-0.7% (-2.1% - 0.7%)
Peritoneal effusion	0	1 (0.7%)	-0.7% (-2.1% - 0.7%)
Delayed gastric emptying	1 (0.7%)	0	0.7% (-0.7% - 2.1%)
Patients with CRG complications	42 (30.0%)	46 (32.9%)	-2.9% (-13.8% - 8.0%)
Other complications			
Bleeding	1 (0.7%)	0	0.7% (-0.7% - 2.1%)
Cerebral infarction	0	1 (0.7%)	-0.7% (-2.1% - 0.7%)
Urinary tract infection	2 (1.4%)	1 (0.7%)	0.7% (-1.7% - 3.1%)
Renal failure	0	1 (0.7%)	-0.7% (-2.1% - 0.7%)
Wound infection	3 (2.1%)	2 (1.4%)	0.7% (-2.4% - 3.8%)
Bacteremia	2 (1.4%)	3 (2.1%)	-0.7% (-3.8% - 2.4%)
Sepsis	4 (2.9%)	6 (4.3%)	-1.4% (-5.8% - 3.0%)
Unilateral RLN injury	14 (10.0%)	15 (10.7%)	-0.7% (-7.8% - 6.4%)
Left RLN injury	12 (8.6%)	14 (10.0%)	-1.4% (-8.2% - 5.4%)
Right RLN injury	2 (1.4%)	1 (0.7%)	-0.7% (-1.7% - 3.1%)
Chylothorax	1 (0.7%)	0	0.7% (-0.7% - 2.1%)
Deep venous thrombosis	1 (0.7%)	2 (1.4%)	-0.7% (-3.1% - 1.7%)
Fat necrosis	2 (1.4%)	3 (2.1%)	-0.7% (-3.8% - 2.4%)
Subcutaneous effusion	1 (0.7%)	2 (1.4%)	-0.7% (-3.1% - 1.7%)
Patients with other complications	22 (15.7%)	26 (18.6%)	-2.9% (-11.7% - 5.9%)
Patients with any complication	48 (34.3%)	56 (38.6%)	-4.3% (-15.6 - 7.0%)
Clavien-Dindo grading system			
I	10 (7.1%)	7 (5.0%)	2.1% (-3.5% - 7.7%)
II	21 (15.0%)	24 (17.1%)	-2.1% (-10.7% - 6.5%)
III	12 (8.6%)	14 (10.0%)	-1.4% (-8.2% - 5.4%)

Variable	ITT analysis		
	EOF Group (n = 140)	LOF Group (n = 140)	Difference (95% CI)
IV	5 (3.6%)	11 (7.9%)	-4.3% (-9.7% – 1.1%)
ICU re-admission	5 (3.6%)	9 (6.4%)	-2.8% (-7.9% – 2.3%)
Use of therapeutic decompression tube	8 (5.7%)	11 (7.9%)	-2.2% (-8.1% – 3.7%)
Unscheduled re-admission within 30 days	2 (1.4%)	1 (0.7%)	0.7% (-1.7% – 3.1%)
In-hospital mortality	0	0	-
30-day mortality	0	0	-

Abbreviations: ITT = intention-to-treat; EOF = early oral feeding; LOF = late oral feeding; CI = confidence interval; ARDS = acute respiratory distress syndrome; CRG = cardiac, respiratory and gastrointestinal; RLN = recurrent laryngeal nerve; ICU = intensive care unit

TABLE 3

Perioperative recovery outcomes in the two groups

Variable	EOF Group (n = 140)	LOF Group (n = 140)	P
Time to first flatus (days)	2 (2–3)	3 (2–3)	0.001
Time to first bowel movement (days)	3 (3–4)	4 (3–4)	< 0.001
Length of postoperative stay (days)	7 (7–8)	10 (9–12)	< 0.001

Abbreviations: EOF = early oral feeding; LOF = late oral feeding

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TABLE 4

Quality of life scores between the two groups at six time points^{*}.

Questionnaire Scales and Items	Pre			2 W			4 W			8 W			12 W			24 W		
	EOF (n = 140)	LOF (n = 140)	P	EOF (n = 130)	LOF (n = 128)	P	EOF (n = 132)	LOF (n = 126)	P	EOF (n = 130)	LOF (n = 131)	P	EOF (n = 128)	LOF (n = 130)	P	EOF (n = 124)	LOF (n = 126)	P
EORTC QLQ-C30																		
Global quality of life	74.6 ± 11.8	73.2 ± 13.0	0.346	58.8 ± 15.1	52.6 ± 16.2	0.002	64.2 ± 13.6	54.0 ± 19.2	< 0.001	66.0 ± 12.4	64.1 ± 15.0	0.266	68.9 ± 13.4	66.5 ± 14.6	0.170	70.7 ± 12.6	68.5 ± 14.6	0.204
Functional scales																		
Physical function	96.0 ± 4.0	97.0 ± 7.0	0.143	79.6 ± 13.9	75.2 ± 15.6	0.017	84.2 ± 10.9	85.2 ± 15.3	0.545	86.1 ± 12.9	85.7 ± 14.9	0.817	89.6 ± 13.7	86.5 ± 16.7	0.105	92.6 ± 14.7	89.5 ± 14.8	0.098
Role function	96.3 ± 12.5	95.7 ± 14.2	0.708	68.3 ± 22.0	64.7 ± 19.5	0.166	74.3 ± 16.4	73.4 ± 17.9	0.674	78.8 ± 16.4	81.7 ± 15.0	0.137	84.8 ± 16.0	85.1 ± 15.7	0.879	86.8 ± 16.5	88.1 ± 15.8	0.525
Emotional function	83.6 ± 13.5	84.5 ± 18.1	0.638	65.1 ± 14.7	55.0 ± 17.2	< 0.001	72.1 ± 10.7	70.3 ± 13.0	0.225	80.5 ± 11.2	78.7 ± 13.6	0.274	83.6 ± 13.3	84.9 ± 16.9	0.493	88.2 ± 14.3	87.9 ± 13.9	0.867
Cognitive function	96.0 ± 9.2	95.3 ± 12.3	0.590	80.8 ± 9.7	78.7 ± 13.0	0.142	83.3 ± 13.3	84.4 ± 11.6	0.480	85.0 ± 14.7	88.3 ± 12.5	0.052	89.8 ± 16.3	90.1 ± 14.6	0.876	90.8 ± 14.3	89.2 ± 13.6	0.366
Social function	76.1 ± 16.7	76.0 ± 18.0	0.962	65.6 ± 14.3	58.5 ± 16.5	< 0.001	68.4 ± 13.4	66.2 ± 13.1	0.184	70.7 ± 15.3	68.4 ± 13.4	0.197	73.6 ± 12.6	74.2 ± 14.5	0.723	78.6 ± 14.6	78.2 ± 12.9	0.819
General symptom scales																		
Fatigue	14.1 ± 10.8	14.5 ± 11.9	0.769	35.7 ± 15.4	48.7 ± 14.2	< 0.001	30.7 ± 15.2	33.9 ± 16.8	0.110	26.6 ± 13.4	27.7 ± 14.4	0.524	20.4 ± 11.3	21.1 ± 13.0	0.645	18.6 ± 12.6	20.1 ± 15.6	0.404
Nausea and vomiting	8.7 ± 6.5	8.5 ± 6.7	0.800	26.9 ± 12.1	38.6 ± 14.2	< 0.001	22.3 ± 9.2	26.8 ± 13.2	0.002	18.6 ± 12.8	19.8 ± 11.2	0.421	16.9 ± 8.6	17.7 ± 11.8	0.535	14.9 ± 12.6	16.7 ± 14.8	0.302
Pain	8.0 ± 7.0	7.8 ± 6.1	0.799	27.2 ± 14.6	34.4 ± 16.6	< 0.001	21.4 ± 13.1	24.1 ± 14.4	0.116	17.7 ± 12.9	20.2 ± 12.6	0.115	14.0 ± 13.7	15.8 ± 14.5	0.307	12.6 ± 11.2	13.2 ± 12.1	0.542
General symptom items																		
Dyspnea	10.9 ± 12.8	9.8 ± 11.3	0.477	23.3 ± 16.7	25.1 ± 18.1	0.407	21.7 ± 16.3	19.2 ± 16.0	0.215	16.9 ± 12.0	15.0 ± 13.7	0.235	14.9 ± 12.3	13.0 ± 10.7	0.187	12.6 ± 12.8	10.0 ± 12.2	0.101
Insomnia	5.8 ± 12.0	5.2 ± 13.4	0.693	24.9 ± 19.5	26.4 ± 18.0	0.522	19.8 ± 17.4	18.2 ± 15.9	0.442	16.5 ± 12.6	15.3 ± 12.3	0.437	14.5 ± 12.5	16.4 ± 12.0	0.214	13.5 ± 11.5	14.4 ± 12.6	0.556
Appetite loss	4.9 ± 11.9	5.2 ± 12.1	0.835	20.9 ± 16.4	27.4 ± 18.4	0.003	22.4 ± 16.8	24.2 ± 17.5	0.400	20.4 ± 14.6	23.6 ± 16.2	0.095	16.4 ± 14.4	18.3 ± 12.3	0.255	14.4 ± 11.4	16.3 ± 13.8	0.237
Constipation	5.5 ± 8.4	6.3 ± 9.5	0.456	16.4 ± 14.8	16.2 ± 13.4	0.910	12.9 ± 13.4	14.0 ± 12.4	0.495	15.2 ± 12.2	13.1 ± 14.2	0.201	12.0 ± 12.3	12.4 ± 12.7	0.797	11.8 ± 10.3	11.4 ± 10.8	0.765
Diarrhea	6.9 ± 12.8	7.8 ± 10.3	0.517	14.9 ± 14.1	25.9 ± 12.7	< 0.001	17.4 ± 12.7	21.0 ± 14.9	0.037	15.4 ± 14.0	16.4 ± 13.1	0.552	16.9 ± 12.8	14.6 ± 12.3	0.142	12.9 ± 12.2	12.6 ± 11.3	0.840
Financial difficulties	16.2 ± 9.1	15.1 ± 9.8	0.331	48.3 ± 18.5	51.6 ± 19.8	0.168	39.3 ± 16.5	37.1 ± 17.9	0.305	33.3 ± 15.0	31.9 ± 13.5	0.429	29.4 ± 14.9	29.6 ± 14.3	0.906	21.4 ± 12.9	22.6 ± 13.3	0.470
EORTC QLQ-OES18																		
Esophageal-specific symptom scales																		
Dysphagia	28.6 ± 19.0	25.7 ± 19.4	0.207	32.5 ± 12.5	48.4 ± 19.8	< 0.001	26.2 ± 15.8	28.9 ± 16.9	0.186	20.0 ± 16.4	19.0 ± 16.4	0.623	17.7 ± 14.3	20.4 ± 13.7	0.123	18.7 ± 14.9	20.9 ± 14.7	0.241
Eating difficulties	19.2 ± 9.1	18.1 ± 9.6	0.326	28.1 ± 11.9	34.6 ± 20.2	0.002	24.4 ± 11.7	27.6 ± 17.6	0.085	22.4 ± 12.0	23.4 ± 14.0	0.536	16.2 ± 12.9	19.0 ± 11.9	0.071	18.2 ± 10.9	16.0 ± 12.9	0.147
Reflux	10.4 ± 17.4	10.1 ± 17.5	0.887	16.4 ± 17.0	18.5 ± 17.3	0.326	17.4 ± 16.8	19.7 ± 17.2	0.278	22.4 ± 17.6	21.4 ± 15.6	0.628	28.9 ± 15.0	26.7 ± 16.1	0.257	32.9 ± 15.8	29.7 ± 16.5	0.119
Esophageal pain	9.5 ± 8.4	10.3 ± 9.5	0.456	23.5 ± 6.5	25.3 ± 8.4	0.055	21.1 ± 12.2	23.3 ± 16.6	0.225	15.5 ± 9.2	15.8 ± 9.4	0.795	14.8 ± 9.8	15.0 ± 9.7	0.869	11.8 ± 9.8	12.0 ± 8.7	0.865
Esophageal-specific items																		
Trouble swallowing saliva	9.9 ± 12.0	9.0 ± 10.8	0.510	14.9 ± 12.2	24.1 ± 16.2	< 0.001	12.9 ± 13.5	15.0 ± 13.8	0.218	11.9 ± 12.7	12.0 ± 13.1	0.950	10.9 ± 11.9	12.1 ± 11.6	0.4129	11.6 ± 10.9	12.6 ± 13.6	0.522

Questionnaire Scales and Items	Pre		2 W		4 W		8 W		12 W		24 W		P					
	EOF (n = 140)	LOF (n = 140)	P	EOF (n = 130)	LOF (n = 128)	P	EOF (n = 132)	LOF (n = 126)	P	EOF (n = 130)	LOF (n = 131)	P		EOF (n = 124)	LOF (n = 126)			
Choking when swallowing	16.9 ± 11.2	16.7 ± 12.4	0.888	12.0 ± 8.0	11.5 ± 10.7	0.671	10.2 ± 12.4	9.9 ± 10.3	0.833	9.9 ± 8.4	8.5 ± 7.6	0.159	9.0 ± 6.0	8.5 ± 6.6	0.525	9.6 ± 8.0	10.5 ± 9.6	0.917
Dry mouth	18.4 ± 16.1	18.8 ± 17.4	0.842	27.9 ± 17.6	29.6 ± 15.5	0.411	18.9 ± 15.4	19.7 ± 16.0	0.683	17.9 ± 16.4	16.0 ± 15.7	0.340	15.9 ± 12.7	14.6 ± 12.1	0.4006	15.4 ± 10.4	13.6 ± 11.1	0.187
Trouble with taste	6.0 ± 12.5	6.1 ± 10.6	0.943	15.4 ± 13.5	14.6 ± 12.9	0.627	13.4 ± 10.0	13.1 ± 11.3	0.821	13.0 ± 8.0	12.9 ± 9.9	0.929	12.0 ± 12.5	11.5 ± 10.4	0.7270	9.8 ± 9.5	10.5 ± 10.4	0.585
Trouble with coughing	6.0 ± 7.1	5.8 ± 8.9	0.836	18.9 ± 12.7	17.6 ± 10.8	0.377	17.9 ± 12.6	18.2 ± 12.7	0.849	16.9 ± 14.7	14.4 ± 13.8	0.158	15.0 ± 11.4	13.9 ± 12.6	0.463	12.0 ± 11.4	11.9 ± 10.6	0.943
Speech difficulties	4.0 ± 6.0	4.4 ± 6.3	0.587	14.4 ± 9.4	16.7 ± 10.6	0.066	12.9 ± 10.2	12.2 ± 10.5	0.588	11.0 ± 9.7	12.0 ± 10.3	0.420	10.0 ± 12.9	10.6 ± 12.6	0.706	8.0 ± 8.9	7.6 ± 9.6	0.733

*The scores are presented as the mean ± standard deviation.

Abbreviations: EOF = early oral feeding; LOF = late oral feeding; EORTC = European Organization for Research and Treatment of Cancer