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Original Research Article

Preoperative Elemental Diet before Laparoscopic Anterior Resection in Patients with Advanced Stenotic Rectal Cancer

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Abstract

Objectives: To evaluate the feasibility of our new preoperative enteral nutrition protocol using Elental® without mechanical bowel preparation (MBP) before laparoscopic anterior resection (LAR) in patients with advanced stenotic rectal cancer.

Methods: Among 74 patients with advanced rectal cancer (clinical stages T3 and T4) scheduled to undergo LAR, 42 patients with stenotic rectal cancer were administered Elental® (900 kcal/day) without MBP before LAR (group S). Thirty-two patients without stenosis (group NS) did not receive preoperative nutritional support but underwent MBP.

Results: Group S patients were maintained in a fasting state and received an elemental diet approximately 10 days preoperatively without severe adverse effects. The incidence of postoperative complications (Clavien-Dindo classification ≥ grade 2) was significantly lower in group S than that in group NS (adjusted odds ratio [OR]: 6.046, P = 0.008). Logistic regression analysis revealed that group NS exhibited higher risks of developing postoperative complications than those exhibited by group S (OR: 4.32, 95% confidence interval [CI]: 1.28-17.28, P = 0.018). Among preoperative characteristics, the clinical tumor stage indicated a significant intergroup difference. Thus, the clinical stage was selected as a covariate and adjusted in the logistic regression model to calculate a covariate-adjusted OR. Group NS exhibited a higher incidence of postoperative complications than group S (adjusted OR: 6.05, 95% CI: 1.58-28.35, P = 0.008).

Conclusions: Administration of an elemental diet using Elental® without MBP before LAR is a feasible strategy in patients with advanced stenotic rectal cancer. Application of this research may encourage use of Elental® in the clinical setting.

Keywords
elemental diet, laparoscopy, rectal cancer, stenosis

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Introduction

Although laparoscopic rectal resection has recently become common worldwide because of its beneficial effect on postoperative outcomes[1], evidence regarding its efficacy and oncological safety has not been conclusively established[2]. One of the reasons for the difficulty in achieving favorable oncologic results in rectal cancer is the difficulty of the surgical technique, particularly for rectal cancer patients with stenotic tumors. Patients with stenotic rectal cancer often develop bowel obstruction. In cases of complete bowel obstruction, urgent treatments such as stents or diverting stomas are necessary. If the large bowel is severely but not completely obstructed, patients are generally required to

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be in a fasting state to retain bowel rest and are given total parenteral nutrition.

Malnutrition has been considered a risk factor for postoperative complications such as anastomotic leakage and surgical site infection[3]. Several meta-analyses have demonstrated that enteral nutrition decreases the risk of complications compared with parenteral nutrition[4-6]. Ideally, patients with stenotic rectal cancer should not receive total parenteral nutrition, but enteral nutrition should be used instead, even if the tumors are stenotic. Elental® (EA Pharma Co., Inc., Tokyo, Japan) is an elemental diet that has been used in patients with inflammatory bowel disease[7,8] or chemotherapy-induced oral mucositis[9]. Elental® is composed of amino acids and contains only small amounts of fatty acids. It produces little food residue after digestion, thereby reducing the burden on the digestive system[10,11]. Thus, we postulated that patients with stenotic rectal cancer undergoing anterior resection could safely take the elemental diet even if they had stenotic tumors. It is essential to evaluate the efficacy and safety of preoperative enteral nutrition protocols preceding rectal resection. Currently, rectal surgery is performed laparoscopically. Therefore, examination of the effectiveness and safety of the enteral nutrition protocol before laparoscopic rectal resection is crucial.

We hypothesized that a preoperative elemental diet protocol using Elental® could be a safe and effective nutritional strategy for patients with stenotic rectal cancer and could decrease postoperative complications. This retrospective case-control study evaluated the efficacy and safety of our novel preoperative elemental nutrition protocol before laparoscopic anterior resection (LAR) in patients with advanced stenotic rectal cancer.

Methods

Patients

We retrospectively examined all consecutive patients who underwent elective LAR for primary advanced rectal cancers (clinical stages T3 and T4 [cT3 and T4]) between December 2012 and September 2017 at Hokkaido University Hospital. Patients were classified into two groups: stenotic tumors (group S) and non-stenotic tumors (group NS). Stenotic tumors were defined as tumors in which a colonoscope could not be inserted owing to stenosis. Patients who required insertion of long tubes, those with diverting stomas or stents owing to complete bowel obstruction, or those who refused the elemental diet were excluded. The extent of lymph node dissection and cancer stage were classified based on the 2014 Japanese Society for Cancer of the Colon and Rectum Guidelines[12]. The institutional review board of Hokkaido University Hospital approved the study protocol (approval number: 015-0451). This study was performed according to the Declaration of Helsinki. Patients were not required to provide informed consent because the analysis used anonymous clinical data. For complete details regarding disclosure, the study details have been published on the home page of Hokkaido University Hospital.

Study 1

At our department, all patients with stenotic rectal cancer without complete bowel obstruction (group S) received a preoperative elemental diet. Group S patients started fasting upon admission. The elemental diet was administered from the time of admission until the day before surgery, and if necessary, rehydration therapy was added. A pack of Elental® containing 300 kilocalories (kcal) was dissolved in 300 mL of water for oral administration. Most patients were administered the elemental diet with flavored powder added to the solution to improve the taste. The oral dose of the elemental diet was gradually increased from 2 packs/day (600 kcal) on day 1 to 3 packs/day (900 kcal) thereafter. Patients were allowed to drink water, tea, or juice, but access to all other foods was restricted. Patients did not undergo mechanical bowel preparation (MBP). Abdominal radiography and blood tests were performed twice weekly for evaluation. Patients who developed bowel obstruction, peritonitis, dehydration, or electrolyte abnormalities were administered rehydration therapy, and if necessary, the elemental diet was discontinued in such patients.

The hypothesis tested in Study 1 was that the preoperative elemental protocol without MBP could be a safe and feasible strategy to provide nutritional support for group S patients. The rate of completion of the elemental diet protocol and the incidence of adverse effects were examined. The prognostic nutritional index (PNI) was used to evaluate the nutritional status of patients and the risk of operative complications. The PNI was calculated using the formula: 10 × serum albumin value (g/dL) + 0.005 × total lymphocyte count (TLC) of peripheral blood[13,14].

Study 2

We also examined the feasibility of the elemental diet protocol by comparing postoperative outcomes including the incidence of postoperative complications between groups S and NS in Study 2.

Group NS patients did not receive preoperative nutritional support, began fasting after lunch the day preceding surgery, and underwent MBP using polyethylene glycol electrolyte lavage solution (PEG-ELS).

LAR was performed or supervised by a fully certified laparoscopic surgeon (S.H.)[15]. Surgeons qualified by the Endoscopic Surgical Skill Qualification System, which was developed by the Japan Society for Endoscopic Surgery, were selected for performing low anterior resection[16]. The operative procedure was performed using a conventional la-

Table 1. Preoperative Patient Characteristics.

Variable	Group S (n = 42)	Group NS (n = 32)	p-value
Age (years)	64.7 ± 11.2	64.3 ± 11.8	0.889
Men	24 (57)	18 (56)	0.939
BMI (kg/m^2)	22.4 ± 3.5	23.2 ± 3.9	0.310
ASA-PS ≤II	39 (93)	29 (91)	0.729
ECOG-PS 0	29 (69)	26 (81)	0.229
Brinkman index	390 ± 68.5	393 ± 76.5	0.976
History of laparotomy	10 (24)	8 (26)	0.845
Preoperative chemotherapy	2 (5)	5 (16)	0.228
Comorbidity (HT, DM, heart disease, respiratory disease, and brain disease)	10/7/3/2/1 (24/17/7/5/2)	7/4/2/3/3 (22/13/6/7/7)	0.665
Tumor location (Rs/Ra/Rb)	34/8/0 (81/19/0)	22/7/3 (69/22/9)	0.065
Clinical stage ≥IIIa	26 (62)	11 (34)	0.018

The values are presented as means ± standard deviations or numbers (percentages).
Group S: patients with stenotic tumors, group NS: patients with non-stenotic tumors, ASA-PS: American Society of Anesthesiologists' Physical Status, BMI: body mass index, DM: diabetes mellitus, ECOG-PS: Eastern Cooperative Oncology Group performance status, HT: hypertension

paroscopic technique. Dissection was performed using a standard medial-to-lateral approach. The inferior mesenteric artery was ligated at its root in a routine manner. After total mesorectal excision, the rectum was dissected and extracted through an umbilical incision created in the abdominal wall. A double-stapling technique was used to perform colorectal anastomosis. Covering ileostomy was performed in patients who underwent intra-anal canal anastomosis or who had a positive air leak test. Drainage tubes were routinely placed in the pelvis. The umbilical incision was closed using epidermal sutureless closure[17].

Statistical analysis

Data were prospectively collected and retrospectively analyzed. The baseline summary statistics are presented as means ± standard deviations and percentages. Patient characteristics were summarized and statistically tested using Pearson's chi-squared and Fisher's exact tests. The significance level was set at 5% (two-sided) for all statistical tests. Among patient characteristics, the variable exhibiting a statistically significant intergroup difference was considered to be a covariable. The percentage of complications between the groups was compared and statistically tested based on a binomial distribution (normal approximation). The selected variable from Table 1 was chosen as the covariate and adjusted in the logistic regression model to calculate a covariable-adjusted odds ratio (OR) in Study 2. The adjusted OR was calculated using logistic regression analysis, with the clinical stage as a covariable. All statistical calculations were performed using the software package JMP Pro Version 12 (SAS Institute Inc., Cary, NC, USA).

Results

Patient flow and characteristics

During the analysis period, 78 elective LARs were performed to treat primary advanced rectal cancers (cT3 and T4). Among 46 patients with stenotic rectal cancer, four were excluded from the analysis: Three refused the elemental diet, and one required insertion of a long tube. Thus, 42 patients in group S were eligible for analysis in Study 1. Forty-two patients in group S and 32 patients in group NS who underwent LAR were eligible for analysis in Study 2 (Figure 1). In the NS group, tumors tended to be located at a lower level of the rectum compared to those in the S group. There was a significant difference in the distribution of clinical stages in the S and NS groups (Table 1).

Outcomes of Study 1

The preoperative elemental diet was administered to all group S patients from the day of admission until the day before surgery. Forty (95%) patients completed the elemental diet protocol as scheduled. The mean dosing period of the elemental diet was approximately 10 days (10.6 ± 6.1 days). Eight patients required additional rehydration therapy (535.7 ± 744.0 mL/day). As a result, the total calorie intake with the protocol averaged to 1007.1 ± 176.1 kcal/day. After approximately 10 days of elemental diet administration, the PNI of group S patients decreased by 44.1 ± 5.8, which was not significantly different from the values recorded at the time of admission. Although patients lost body weight during the elemental diet intake, the rate of change in body weight was only −2.7%. Local peritonitis occurred in two patients because of tumor penetration into the mesorectum. Peritonitis resolved in both patients after administering anti-

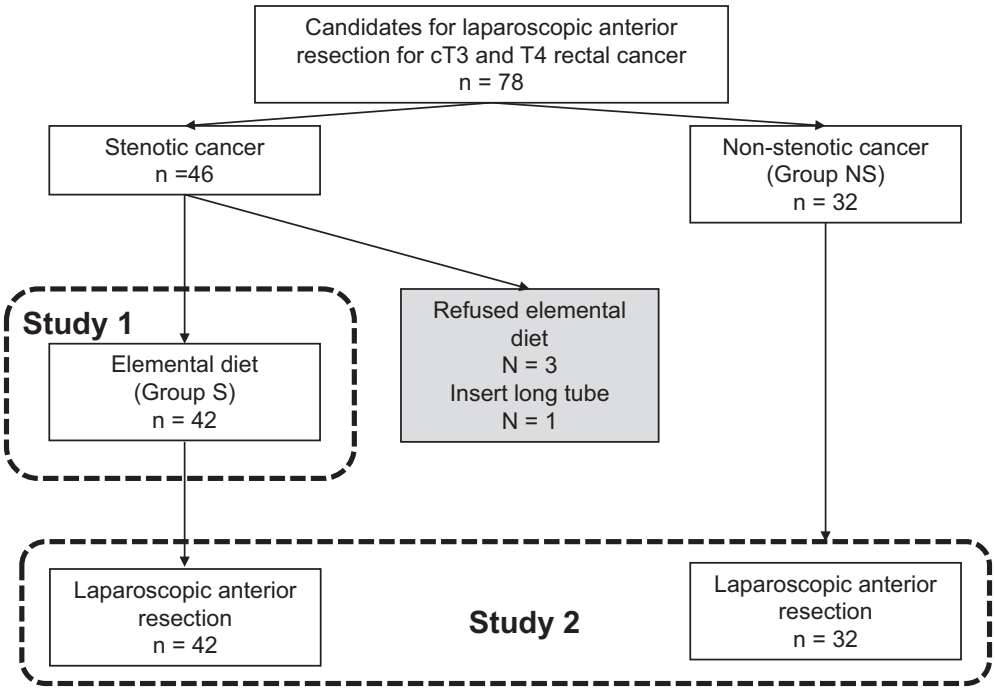

Figure 1. Seventy-eight elective rectal resections performed for highly advanced rectal cancers (cT3 and T4) from December 2012 to September 2017.
Four patients were excluded from the study: Three refused the elemental diet, and one required insertion of a long tube. Forty-two patients with severe stenotic rectal cancers were treated with a preoperative elemental diet (Elental®) (group S). The other 32 patients were assigned to the control group (group NS).

Table 2. Preoperative Elemental Diet and Nutrition.

Preoperative event	Group S (*n* = 42)
Completion of elemental diet	40 (95)
Administration of Elental® (days)	10.6 ± 6.1
Additional rehydration therapy	8 (19)
Additional rehydration volume (mL/day)	535.7 ± 744.0
Total calorie intake (kcal/day)	1007.1 ± 176.1
PNI[a] on admission	48.3 ± 5.9
PNI after Elental® intake	44.1 ± 5.8
Change rate of PNI (%)[b]	−8.6 ± 14.1
Body weight on admission (kg)	59.6 ± 11.5
Body weight after Elental® intake (kg)	58.0 ± 10.8
Change rate of body weight (%)[c]	−2.7 ± 2.5
Adverse effect associated with Elental® intake	
Local peritonitis	2 (4.8)
Complete bowel obstruction	0
Enteritis	0

The results are presented as means ± standard deviations or numbers (percentages).
PNI: prognostic nutrition index; group S, patients with stenotic tumors
[a] PNI = 10 × serum albumin (g/dL) + 0.005 × lymphocyte count (/μL)
[b] Change rate of PNI (%) = ([PNI after Elental® intake] − [PNI on admission]) / [PNI on admission] × 100
[c] Change rate of body weight (%) = ([body weight after Elental® intake] − [body weight on admission]) / [body weight on admission] × 100

biotics and withdrawing the elemental diet. No patient developed complete bowel obstruction or obstructive enteritis during the course of the nutritional treatment (Table 2).

Outcomes of Study 2

Operative procedure

The operative procedures were similar between the two groups (Table 3). Four (10%) and six (19%) patients in groups S and NS, respectively, underwent simultaneous resection of other organs. One patient (2.5%) in group S required conversion to laparotomy (secondary to invasion of other organs), as did one patient (3.1%) in group NS (secondary to severe adhesions). Five (12%) and six (19%) patients in groups S and NS, respectively, underwent covering ileostomy. No patient in either group reported fecal spillage secondary to poor bowel preparation during anastomosis. The operative time (190.8 ± 57.6 vs. 228.8 ± 98.8 min, P = 0.041) and anesthesia time (292.1 ± 69.7 vs. 333.8 ± 109.8 min, P = 0.049) were significantly shorter in group S than those in group NS. Moreover, the estimated blood loss was lower (10.2 ± 23.5 vs. 31.7 ± 67.1 g, P = 0.058) in group S than in group NS. By contrast, the intraoperative infusion volumes were nearly equivalent between the two groups.

The recovery of bowel movements was satisfactory in both groups. Although the starting dates for fluid admini-

Table 3. Operative Outcomes.

Outcome	Group S (n = 42)	Group NS (n = 32)	p-value
Operative procedure			0.428
High anterior resection	20 (48)	15 (47)	
Low anterior resection	22 (52)	16 (50)	
Total proctocolectomy	0	1 (3.1)[a]	
Other organ resection	4 (10)	6 (19)	0.252
Conversion to laparotomy	1 (2.5)	1 (3.1)	0.846
Covering ileostomy	5 (12)	6 (19)	0.414
Qualified surgeon by ESSQS	22 (59)	21 (66)	0.251
Spillage of feces	0	0	
D3 lymph node dissection	39 (93)	28 (88)	0.438
Number of dissected lymph nodes	24.1 ± 9.86	18.4 ± 12.4	0.031
Operative time (min)	191 ± 57.6	229 ± 98.8	0.041
Anesthesia time (min)	292 ± 69.7	334 ± 109.8	0.049
Estimated blood loss (g)	10.2 ± 23.5	31.7 ± 67.1	0.058
Intraoperative infusion volume (mL)	1,838 ± 575	1,941 ± 997	0.576
First day of passing flatus (PODs)	2.31 ± 0.19	2.31 ± 0.22	0.992
First day of defecation (PODs)	3.17 ± 0.34	3.59 ± 0.39	0.412
Commencement day for drinking (PODs)	1.03 ± 0.18	1.05 ± 0.22	0.728
Commencement day for eating (PODs)	6.29 ± 1.44	5.84 ± 1.69	0.228
Postoperative hospitalization (days)	13.0 ± 3.40	15.6 ± 6.81	0.034
Readmission within 30 days after discharge	0	1 (3.1)[b]	0.193

The results are presented as means ± standard deviations or numbers (percentages).

Group S: patients with stenotic tumors, group NS: patients with non-stenotic tumors, ESSQS, Endoscopic Surgical Skill Qualification System; PODs, postoperative days

[a] Rectal cancer associated with ulcerative colitis

[b] One case of small bowel obstruction

stration and diet resumption were similar between the two groups, the duration of postoperative hospitalization was significantly shorter in group S than that in group NS (13.0 ± 3.40 vs. 15.6 ± 6.81 days, P = 0.034). None of the patients in group S required readmission within 30 days postoperatively, whereas one patient in group NS had to be readmitted (secondary to small bowel obstruction) (Table 3). There was no substantial difference in perioperative inflammatory responses, including white blood cell (WBC) count (Figure 2a), C-reactive protein level (Figure 2b), and the neutrophil-to-lymphocyte ratio (NLR). However, the WBC count on postoperative day (POD) 7 was significantly lower in group S than that in group NS (Figure 2c). Although the PNIs in group S were lower than those in group NS, they recovered to their preoperative levels on POD 7 (Figure 2d).

Tumor characteristics

Intergroup differences were observed in terms of tumor characteristics. The maximum tumor diameter (55.2 ± 16.7 vs. 39.8 ± 16.8 mm, P < 0.001) and tumor diameter/large bowel circumference ratio (82.8 ± 19.1 vs. 48.9% ± 24.7%, P < 0.001) were significantly greater in group S than those in group NS. However, the percentage of patients showing pathological T4, ≤N1, and stage, and the distal surgical margin were similar between the two groups. None of the patients in either group showed circumferential margin positivity. Furthermore, the oral/anal side (2 cm from the tumor edge) ratios of the large bowel circumference were similar between the groups, as presented in Table 4.

Postoperative complications

The incidence of postoperative complications (Clavien-Dindo classification grade ≥2) was significantly lower in group S than that in group NS (P = 0.018). None of the patients in either group developed anastomotic leakage or required re-operation secondary to postoperative complications (Table 5). We performed logistic regression analysis to confirm whether the preoperative elemental diet reduced postoperative complications. Patients in group NS had a higher risk of developing postoperative complications (OR: 4.32, 95% CI: 1.28-17.28, P = 0.018). Among patients' preoperative characteristics, however, the clinical tumor stage had a significant intergroup difference. Thus, the clinical stage was the variable selected as a covariate and was adjusted in the logistic regression model to calculate a covariate-adjusted OR. Group NS had a higher rate of postoperative complications than that in group S (adjusted OR: 6.05, 95% CI: 1.58-28.35, P = 0.008), as listed in Table 6.

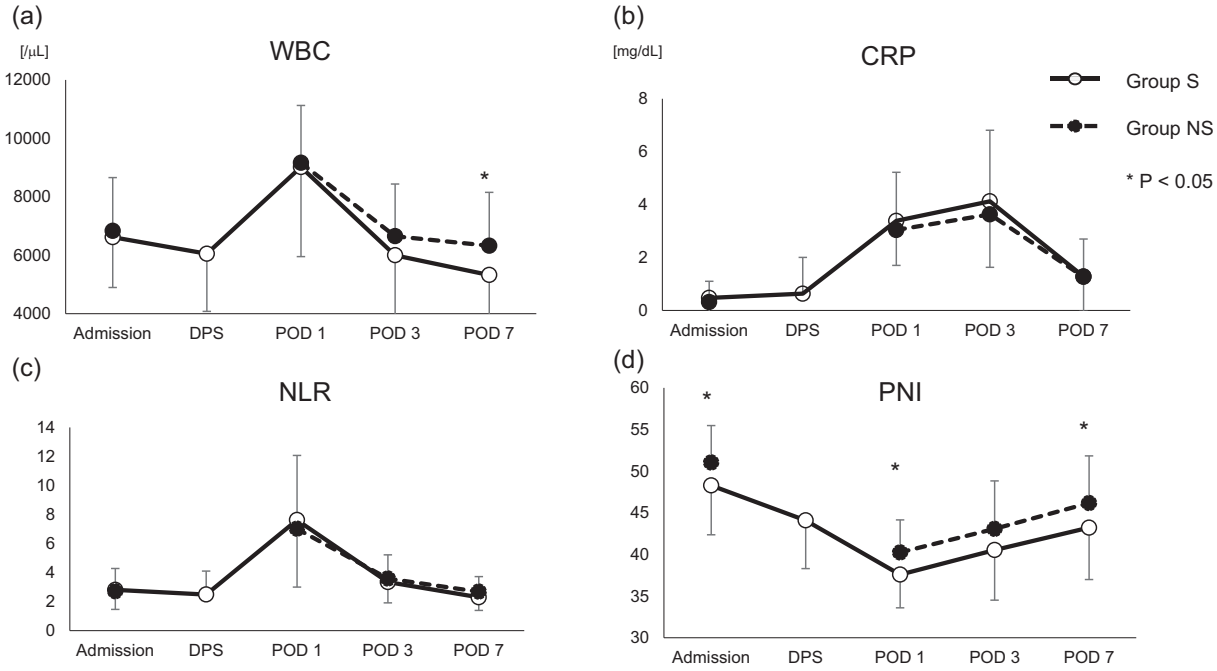

Figure 2. Perioperative inflammatory reaction and nutrition status.

The parameters of perioperative inflammatory reaction and nutritional status are shown. Preoperative blood tests were performed on admission, and values on the day preceding surgery were missing in group NS. Values are presented as means ± standard deviations.

Group S: patients with stenotic cancer, group NS: patients with non-stenotic cancer, WBC: white blood cell, CRP: C-reactive protein, NLR: neutrophil-to-lymphocyte ratio, PNI: prognostic nutrition index, POD: postoperative day, DPS: the day prior to surgery

Table 4. Tumor Characteristics.

Tumor factor	Group S (n = 42)	Group NS (n = 32)	p-value
Maximum tumor diameter (mm)	55.2 ± 16.7	39.8 ± 16.8	<0.001
Tumor diameter/circumference of the large bowel ratio (%)	82.8 ± 19.1	48.9 ± 24.7	<0.001
Histological type (tub1+tub2)	40 (95)	29 (91)	0.436
Pathological T4	11 (26)	1 (3)	0.004
Pathological ≤N1	22 (52)	13 (41)	0.315
Pathological stage ≤IIIa	25 (60)	15 (47)	0.279
Distal margin (mm)	38.9 ± 26.7	44.9 ± 36.4	0.417
Circumferential margin positive (%)	0	0	
Large bowel circumference on the oral side/anal side of the tumor[a, b] (%)	94.2 ± 14.1	97.4 ± 15.7	0.341

The results are presented as means ± standard deviations or numbers (percentages).

Group S: patients with stenotic tumors, group NS: patients with non-stenotic tumors

[a] Ratio = circumference on the oral side (2 cm away from tumor)/circumference on the anal side (2 cm away from tumor edge)

[b] Excluded were cases in which the circumference could not be measured: The proximal or distal margin was <2 cm.

Discussion

This study describes the first reported use of preoperative enteral nutrition with the administration of Elental® in patients with advanced (cT3 and T4) stenotic rectal cancer before LAR. The enteral nutrition protocol without MBP was considered safe and feasible for patients with stenotic rectal cancer. The characteristics of our preoperative elemental nutrition protocol can be summarized as follows: Patients were administered fluids and nutritional support without rehydration therapy (if possible). Although the success rate of the enteral nutrition protocol was notably high (95%), the percentage of patients who required additional rehydration therapy was not low (19%). Small quantities of peripheral par-

Table 5. Postoperative Complications.

Postoperative events	Group S (n = 42)	Group NS (n = 32)	*p*-value
Total	4 (10)	10 (31)	0.018
Wound infection	0	1 (3.1)	
Intra-abdominal abscess	1 (2.5)	0	
Colitis	0	1 (3.1)	
Urinary tract infection	1 (2.5)	0	
Bile leakage[a]	0	1 (3.1)	
Hemorrhagic duodenal ulcer	0	1 (3.1)	
Anastomotic leakage	0	0	
Anastomotic hemorrhage	1 (2.5)	1 (3.1)	
Portal vein thrombosis	0	1 (3.1)	
Small bowel obstruction	1 (2.5)	2 (6.3)	
Pulmonary embolism	0	2 (6.3)	
Reoperation	0	0	

Data are presented as numbers (percentages).

Group S: patients with stenotic tumors, group NS: patients with non-stenotic tumors

[a] Associated with liver resection.

Table 6. Logistic Regression Analysis of Patients' Groups for Postoperative Complications.

Groups	Unadjusted		*p*-value	Adjusted		*p*-value
	OR	95% CI		OR	95% CI	
S/NS	4.32	1.28–17.28	0.0178*	6.05	1.58–28.35	0.0080*

The clinical stage is a covariable for the adjusted odds ratio in logistic regression.

S: patients with stenotic tumors, NS: patients with non-stenotic tumors, OR: odds ratio, CI: confidence interval

enteral infusions (approximately 500 mL/day) were beneficial in these patients. No patient developed severe dehydration. The bowel lumen was cleansed without MBP.

The extent/quantity of nutrition delivered is an important consideration in this context. Our protocol included delivery of enteral nutrition amounting to 900 kcal/day in group S patients. The American Society for Parenteral and Enteral Nutrition recommends 1,200-1,500 kcal of preoperative elemental nutrition in malnourished patients (serum albumin levels ≤ 3.5 g/dL) who undergo surgery of the esophagus, stomach, pancreas, or biliary tract[18]. The nutritional support provided by our protocol appears to be insufficient compared with the ideal nutritional requirement. However, Braga et al. reported that 890 mL/day of enteral nutrition was administered to patients who underwent colorectal resection despite being prescribed 1,000 mL/day[19]. We reasoned that patients who received only enteral nutrition would have a negative reaction to consuming ≥1000 mL/day of enteral nutrition fluid. Thus, to improve patient compliance and ensure successful completion of our study, we decided that patients should be given the option of consuming a quantity of fluid of their choice that they were comfortable with, in addition to 900 mL of the elemental diet.

Many nutritional parameters are reported, such as serum total protein, serum albumin, total cholesterol, TLC, rapid turn-over proteins (pre-albumin and transferrin), and PNI. We selected PNI because PNI is calculated using two important nutritional factors (serum albumin and TLC). Previous reports revealed that severe postoperative complications are associated with inflammatory response and malnutrition[20,21]. An inflammatory response in patients with malignancy is also related to the level of serum albumin and TLC[22,23]. Therefore, we evaluated the nutritional status of patients using PNI. A low PNI (≤45.5) was reported to be an independent risk factor for severe postoperative complications[14]. Although the preoperative PNI of group S was 44.1 (lower than 45.5) and could be a risk factor for severe complications, the rate of postoperative complications had no correlation with preoperative PNIs, perhaps because of a relation to other tumor or surgical factors. A previous study reported that resection and anastomosis of the gastrointestinal tract are contraindicated in patients with PNI < 40[13]. In this study, the average PNI in group S patients declined from 48.3% to 44.1% after preoperative administration of

nutritional support. Preoperative PNI in both groups was >40, and no patients developed anastomotic leakage. The rates of preoperative reduction of PNI and body weight were only 8% and 2%, respectively, considering the contribution of enteral nutrition. Furthermore, the intake of an elemental diet led to fewer adverse effects. Thus, we considered that Elental® administration (900 mL/day) for approximately 10 days preoperatively is an acceptable strategy in patients with stenotic rectal cancers scheduled to undergo LAR. However, in patients requiring long-term fasting, total parenteral nutrition and infusion of intravenous lipid emulsion should be considered to compensate for the inability of this protocol to meet dietary requirements and to deliver essential fatty acids[11].

Patients with stenotic cancers are maintained in a fasting state preoperatively and receive parenteral nutrition to prevent the development of complete bowel obstruction. Although total parenteral nutrition provides sufficient fluid volume and nutritional support in fasting patients, interference with the patient's daily activities, additional nursing requirements, catheter-related infections, thrombosis, and complications associated with central venous catheter insertion are distinct disadvantages. Moreover, several meta-analyses have demonstrated that compared with enteral nutrition, parenteral nutrition increases the risk of infectious complications[4-6]. Okamoto et al. demonstrated that a lack of nutrients delivered through enteral nutrition reduced the numbers of T cells and immunoglobulin A-producing cells in the gut-associated lymphoid tissue in patients with colon cancer[24]. A decline in the optimal functioning of the intestinal immune system could allow bacterial translocation and increase the risk of infectious complications[25,26]. Furthermore, Braga et al. reported that preoperative enteral formulas positively modulated postoperative immune and inflammatory responses[27]. In this study, according to the NLR, it was unclear whether enteral nutrition using Elental® improved immune responses. Inflammatory responses are important factors that lead to organ dysfunction and adverse outcomes. The WBC count on POD 7 was significantly lower in group S than that in group NS, and Elental® seemed to decrease postoperative inflammatory responses. Thus, we preferred enteral nutrition for the preoperative management of patients with advanced stenotic rectal cancers.

Patients with stenotic rectal cancer are prone to complete bowel obstruction, which interferes with adequate intraoperative visualization of the operative field such that bowel manipulation becomes significantly more difficult, particularly during laparoscopic surgery. We believed that it was important to safely decrease the stool burden in the bowel lumen as much as possible during administration of enteral nutrition. Generally, the first choice for enteral nutrition in patients with normal intestinal function is the polymeric formula because of its advantages of a higher fat content, pleasant taste, and ideal nutritional balance. Despite a lack of evidence that the polymeric formula is more likely to cause bowel obstruction, the polymeric formula is known to produce more food residue than the elemental diet. Moreover, the osmotic pressure of the elemental diet (760 mOsm/L) is much higher than that of the polymeric formula (330-360 mOsm/L). Further, the elemental diet causes diarrhea and could thus play a role as "a nutritious laxative"[10]. Therefore, the elemental diet has some advantages for patients with stenotic rectal cancer, whereas the polymeric formula has other benefits. The efficacy of preoperative MBP has not been established for LAR, particularly in patients with advanced rectal cancer with stenosis. However, a randomized trial in France indicated that rectal cancer surgery without MBP was associated with a greater risk of overall and infectious morbidity. Therefore, it was recommended that MBP should be performed before elective rectal resection[28]. In cases of poor bowel preparation, the colon is occasionally filled with liquid feces, resulting in spillage into the surgical wound. Preoperative bowel preparation is necessary to prevent infectious complications, particularly in patients with severe stenotic rectal cancer. In this study, despite the omission of MBP, the incidence of infectious morbidity was very low (4.8%) in group S. Moreover, the incidences of thromboembolic complications were different between the groups. The underlying reason for the lower rate of thromboembolic complications in group S is unknown. However, we speculate that the shorter operative time in group S had an impact on the occurrence of thromboembolic complications[29,30]. We propose two reasons for the lower incidence of postoperative complications in group S. One potential reason is that the rate of lower rectal cancer was higher in the group NS than in group S. Although the surgical procedures were not significantly different between the two groups, lower rectal cancer surgery tended to require longer operation time and resulted in greater blood loss. Those surgeries were, therefore, likely to result in increased postoperative complications. The other reason is that MBP with PEG-ELS before LAR is possibly harmful. Although PEG-ELS provides adequate bowel irrigation, the administration of PEG-ELS often causes bowel distention due to edema of the intestine and the swallowing of a large amount of air[31]. By contrast, intestinal wall edema was unlikely to occur in group S because the osmotic pressure of Elental® (760 mOsm/L) was much higher than that of plasma[10]. Moreover, none of the patients in group S developed complete bowel obstruction or obstructive enteritis during the course of enteral nutrition. Notably, the large bowel on the oral side of the tumor was not abnormally dilated, and no interference with adequate visualization of the operative field necessitating conversion into laparotomy was reported in any patient. In group S, the large bowel was successfully

irrigated without MBP, and fecal contamination of the operative field was not reported in any patient. Thus, we believe that Elental® can play an important role in bowel preparation.

We believe that the lower invasiveness in terms of bowel preparation was attributable to the unique characteristics of the Elental® solution, such as high osmotic pressure and low food residue production. Further, we suggest that these characteristics of Elental® ameliorated the patients' preoperative condition and subsequently improved operative and postoperative outcomes. Although several previous reports have demonstrated the usefulness of perioperative elemental nutrition in colorectal surgery, we emphasize that our preoperative elemental diet protocol using Elental® without MBP was safe and effective, even for the management of patients with advanced stenotic rectal cancers[27]. However, two patients in group S developed local peritonitis secondary to tumor-related peritonitis on days 2 and 4 of the protocol; therefore, careful monitoring is necessary during the course of enteral nutrition, particularly during the initial period.

This study had some limitations. First, this was a retrospective study comprising a small number of patients at a single center. Second, ideally, the control group in Study 2 should have comprised patients with stenotic tumors without an elemental diet. However, excluding patients who required emergent bowel decompression therapies such as stents or diverting stomas because of complete bowel obstruction, all patients with stenotic tumors received enteral nutrition at our institution. Thus, we could not compare the incidence of morbidity between patients with stenotic rectal cancer with and without enteral nutrition therapy in this study. Third, the oncological safety of laparoscopic resection has not been clearly established in patients with advanced rectal cancer. Fourth, detailed evaluation of the patients' nutritional statuses, such as data regarding the rapid turnover of protein, was unavailable. Finally, this protocol was contraindicated in patients with heart or renal failure requiring strict adherence to fluid intake restrictions. The elemental nutrition protocol was not applicable to these patients.

In summary, our preoperative elemental nutrition protocol using Elental® without MBP before LAR is a feasible nutritional strategy for patients with advanced stenotic rectal cancer. To validate our results, large-scale prospective studies are required to confirm the efficacy and safety of this protocol prior to LAR.

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Conflicts of Interest

There are no conflicts of interest.

Author Contributions

Tadashi Yoshida, Shigenori Homma, Nobuki Ichikawa, Hiroaki Iijima, and Akinobu Taketomi made substantial contributions to the conception and design, acquisition of data, and/or analysis and interpretation of data. Tadashi Yoshida, Nobuki Ichikawa, and Hiroaki Iijima participated in drafting the article. Shigenori Homma and Akinobu Taketomi participated in critically revising the article for important intellectual content. Tadashi Yoshida, Shigenori Homma, Nobuki Ichikawa, Hiroaki Iijima, and Akinobu Taketomi gave final approval of the version to be published.

Approval by Institutional Review Board (IRB)

The institutional review board of Hokkaido University Hospital approved the study protocol (approval number: 015-0451).

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