

Efficacy of Simple Oral Nutritional Supplements Versus Usual Care in Postoperative Patients with Gastric Cancer: A Multicenter, Open-label, Parallel, Randomized Controlled Trial

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Author contribution:

Kohei Ueno and Tatsuto Nishigori designed the overall framework of the study and were primarily responsible for drafting the manuscript.

Akiyoshi Nakakura took responsibility for the data analysis, contributing to the development of the study protocol and being involved throughout the data analysis process.

All authors have been involved in the study from planning this study. Each author participated in the research meetings, made substantial contributions to conception and design, and acquisition of data.

All authors participated in drafting the article or revising it critically for important intellectual content and gave final approval of the version of the article.

ABSTRACT

Objective: To evaluate the efficacy of a simple oral nutritional supplement (ONS) without excess nutrients on body weight loss (BWL) after gastrectomy in patients with gastric cancer.

Summary Background Data: BWL is commonly observed in the early few months after gastrectomy for gastric cancer. It is uncertain if a simple ONS with usual diet improve postoperative BWL.

Methods: A multicenter randomized controlled trial was conducted across 19 institutions. Patients undergoing curative gastrectomy for gastric cancer were randomized into the ONS or control group. The ONS group received 400 mL (kcal)/day of ONS mainly containing carbohydrates and proteins for 8 weeks postoperatively. The primary endpoint was the percentage of BWL from baseline to postoperative 8 weeks. Secondary endpoints included handgrip strength, hematological parameters, health-related quality of life, dietary intake, and ONS adherence.

Results: The 124 patients were randomized to the ONS group (n = 62) or control group (n = 62), with 2 in the ONS group lost to follow-up. The ONS group experienced significantly less weight loss at postoperative 8 weeks (−4.8% vs. −6.4%, $P = 0.039$). No significant differences were observed in handgrip strength or hematological parameters. The incidences of adverse events were comparable between the groups (7% vs. 11%, $P = 0.373$), but the ONS group had higher

symptom scores for insomnia, appetite loss, and diarrhea during intervention. The mean ONS intake was >75% (308.7 mL $\pm$ 97.0 mL/day).

Conclusions: The simple ONS for 8 weeks after gastrectomy reduced postoperative BWL in patients with gastric cancer.

Keywords: Gastric cancer, Gastrectomy, Oral nutritional supplement, Body weight loss, Patient-reported outcomes

Trial Registration: jRCTs051230012; Japan Registry of Clinical Trials. Registered on Apr. 13, 2023.

INTRODUCTION

Gastric cancer (GC) is one of the leading causes of mortality worldwide,¹ and gastrectomy remains the cornerstone of curative treatment. However, gastrectomy hinders food retention and oral intake capacities, leading to increased body weight loss (BWL), decreased muscle mass,² and decreased health-related quality of life (HRQoL).³ Oral nutritional supplement (ONS) is an important part of postoperative nutritional management. Studies that investigated the impact of ONSs on BWL after gastrectomy in patients with GC have reported inconsistent results,⁴⁻⁸ with some attributing the lack of significant benefit in reducing BWL to low adherence rates of approximately 50%.^{5,6} This suggests that consistent clinical benefits of ONS may require strategies to improve adherence. One factor that might impact adherence is the composition of ONSs (e.g., trace elements, vitamins, n-3 fatty acids or fats), which can influence their flavor, texture, and viscosity.^{9,10} We hypothesized that, compared with a regular diet alone, a regular diet with a simple ONS, mainly containing carbohydrates and proteins, could reduce BWL in patients after gastrectomy by offering better palatability and adherence due to its uncomplicated composition.

Moreover, it is crucial to evaluate ONS from various perspectives to promote ONS use among patients and maintain good adherence. The effects of ONS on physical factors, such as muscle

strength¹¹ and skeletal muscle mass,⁵ and on HRQoL^{5,12} have not been thoroughly examined in patients after gastrectomy for GC. Although some studies have reported positive effects on handgrip strength and HRQoL (e.g., fatigue and appetite loss) in the ONS group,^{11,12} others have found no significant differences in skeletal muscle mass⁵ and HRQoL^{5,8} between the ONS and control groups. Overall, the limited evidence so far is inconsistent. To comprehensively evaluate the efficacy of ONS in these patients, muscle strength and HRQoL should be included as secondary outcome measures.

This study aimed to conduct a randomized controlled trial (RCT) to evaluate the efficacy of a simple ONS on BWL, muscle strength, and HRQoL. The findings may provide insights into optimizing postoperative nutritional management with reliable information.

METHODS

This RCT was organized by the Kyoto Esophageal and Gastric Surgery Study Group (KEGG), and the participants were recruited from 19 affiliated hospitals. The study was approved by the Certified Review Board of the Kyoto University (No. Y0149) and followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.¹³ All participants provided written informed consent. This RCT was a specified clinical trial under the Clinical Research Act

in Japan and sponsored by the Nestle Japan Co., Ltd. (Tokyo, Japan). The trial was conducted in accordance with the principles of the Declaration of Helsinki and local regulations. This RCT protocol has been reported elsewhere¹⁴ and was registered with the Clinical Research Information Service (jRCTs051230012).

Study Design and Participants

This study was designed as an open-label, multicenter, parallel-group, RCT. The trial started in April 2023, and inclusion was completed in January 2024. A two-step recruitment strategy was used. The eligibility criteria were as follows: (1) aged 18–85 years, (2) Eastern Cooperative Oncology Group Performance Status (PS) 0–2, (3) oral intake would be possible postoperatively, (4) pathologically diagnosed epithelial malignancy of stomach, (5) cStage I-IVA or CY1P0, (6) scheduled for radical gastrectomy, and (7) esophageal invasion length ≤ 2 cm or no esophageal invasion. We excluded patients with combined resection, remnant gastric cancer, double cancer, allergy to the intervention product, and severe organ or psychiatric dysfunction preoperatively (first exclusion criteria).

Secondary registration was performed at postoperative days 5–7. At this stage, we also excluded patients with cM1 or R2 resection (except for CY1), those who were unable to begin an oral diet, and those who did not undergo gastrectomy.

Randomization

At the second enrollment, patients were randomly allocated 1:1 into either the control group (usual care) or the ONS group (ONS + usual care) using a computer-generated stratified block randomization. Permuted blocks were stratified by clinical stage (I vs. $\geq$ II) and surgical procedure (total gastrectomy [TG] vs. non-TG). The allocation was revealed to the investigator at the second enrollment via the electronic data capture system. Although the detailed clinical pathway was not standardized across hospitals, patients in both groups received the same clinical care except for ONS intake.

Additional nutritional supplementation was permitted only in the control group, as it was considered ethically appropriate for patients developing malnutrition after surgery. While this may have disadvantaged the experimental (ONS) group, it was deemed an acceptable trade-off, albeit with the possibility of underestimating ONS effects.

In addition, patients in the control group may have altered their nutritional intake behaviors due to trial participation, potentially biasing the results toward the null. As a result, the ONS effect may have been underestimated; however, this bias was also deemed acceptable, given its disadvantage to the experimental group.

Intervention

Patients assigned to the ONS group received two packs of 200-mL volumes of ready-to-drink and recloseable packaging products (ISOCAL[®] clear) per day added to their regular diet, continuing until 8 weeks after surgery. Each 200-mL pack of ISOCAL[®] (Nestle Japan Co., Ltd., Tokyo, Japan) clear contains 200 kcal, 40 g of carbohydrates (dextrins and sucrose), 10 g of whey protein (including milk-derived components), no fat, 166 g of water, and 0 g of sodium. Patients started the intervention as soon as possible after secondary enrollment.

During the intervention period, the patients were required to keep a daily diary (ONS diary) that included the amount of daily ONS consumed. In addition, a short educational video and brochure were provided at the time of intervention initiation. Each investigator monitored and resolved issues and questions about interventions during the hospital stay until discharge. Moreover, the investigators checked the ONS diaries at the outpatient clinic 1 month after surgery to improve adherence and minimize missing data in the ONS diary.¹⁴

Surgical Procedure and Postoperative Management

Clinical and pathological stages of the malignancies were based on the Japanese Classification of Gastric Carcinoma.¹⁵ Patients underwent standard gastrectomy and lymph-node dissection according to the Japanese Gastric Cancer Treatment Guidelines, 6th edition.¹⁶ The standardization of the gastrectomy techniques has been established through the KEGG regular meetings. Surgical approach, reconstructive method, and postoperative management were selected by each surgeon. Patients with pathological stage II or III disease received adjuvant chemotherapy (AC) by S-1 with/without docetaxel or another regimen, usually started within 4–8 weeks.^{17,18}

Outcomes

Evaluations were performed preoperatively and at postoperative 8 weeks. The primary outcome measure was %BWL from baseline to 8 weeks postoperatively ((BW at 8 weeks after surgery – preoperative BW) / preoperative BW). Intention-to-treat (ITT) analyses were adopted. The secondary outcome measures were the change in handgrip strength, hematologic and blood chemistry (hemoglobin, lymphocyte count, albumin), dietary intakes, and HRQoL from baseline to postoperative 8 weeks. Low handgrip strength was defined as less than 18 kg in women and less than 28 kg in men according to the guideline of Asian Working Group for Sarcopenia.¹⁹

Regarding the HRQoL, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30),²⁰ EORTC QLQ-OG25, and the EuroQol-5D-5L²¹ were used.

Moreover, dietary intake, including calories, carbohydrates, proteins, and fats, was assessed by the dietitian(s) serving at 14 of the 19 participating institutions. The larger 66-item Food Frequency Questionnaire (short-FFQ) was used, which was developed for the Japan Public Health Center-based prospective Study for the Next Generation (JPHC-NEXT),²² calculating food and nutrient intake with corresponding software (FFQ NEXT, Kenpakusha, Tokyo, Japan). Adverse events, including postoperative complications occurring after the second recruitment and randomization, were evaluated by the Common Terminology Criteria for Adverse Events ver. 5.0 of the National Cancer Institute of the United States.

In the ONS group, adherence was assessed using daily patient diaries. To ensure a strict and fair evaluation, missing diary entries were treated as zero intakes, although this approach may have led to an underestimation of adherence. The average daily ONS intake was calculated as the total recorded ONS intake divided by the prespecified total number of days after intervention initiation. (approximately 50 days) In addition, the average daily consumption of ONS and the percentage of patients who consumed ≥ 200 mL per day were calculated. To evaluate patient

impression and the palatability of the ONS, we conducted a post-intervention questionnaire survey at 8 weeks after surgery for the ONS group. The questionnaire included items on flavor acceptability, reasons for non-adherence, and free-text impressions. The full English version of the questionnaire is available as Supplemental Digital Content 1, <http://links.lww.com/SLA/F584> (Post-intervention questionnaire).

Sample Size and Statistical Analysis

The results of previous studies^{4,23–26} showed that the estimated mean percentage of the BWL at 8 weeks after surgery for GC was approximately –8%, with a standard deviation of approximately 5.5%. We anticipated that this percentage might be reduced to –5% in the ONS group, with a mean difference of 3%. To detect this difference, this RCT required 106 participants for a two-sided significance level of 0.05 and 80% statistical power. The estimated total sample size was approximately 120 (60 patients per group), assuming a lost to follow-up rate of approximately 10% from the first to second enrollments patients.

The χ^2 test was performed to compare categorical variables, and the *t*-test and Wilcoxon rank sum test was performed to compare continuous variables. To compare HRQoL 8 weeks postoperatively, we performed a multivariable linear regression analysis adjusted for baseline

values. Missing values for some HRQoL items were handled according to the recommendations in the EORTC QLQ scoring manual.²⁷

We performed the following subgroup analyses for primary outcome: Age (18–64 vs. 65–85 years), Sex (male vs. female), BMI (<22 vs. ≥22 kg/m²), Surgical procedure (TG vs. non-TG), pStage (I vs. ≥II), and Postoperative AC (yes vs. no). We used a per protocol set (PPS) to perform sensitivity analyses. We defined PPS as participants who ingested an average of ≥200 mL of the ONS per day. A significance threshold of $P < 0.05$ was adopted for all tests. STATA software (StataCorp, LLC, College Station, Tex) was used to perform all statistical analyses.

RESULTS

Patient enrollment was started in April 2023 and completed in January 2024. Of the 133 patients who were assessed for eligibility, 124 were randomized. After allocation, two participants in the interventional group were lost to follow-up. Finally, 122 participants (ONS group, 60; control group, 62) were included in the analysis. Figure 1 shows the CONSORT flow diagram. After randomization, the two groups were well-balanced in terms of baseline characteristics (Table 1). Robotic surgery was performed for approximately 60% of the participants in each group, and AC was started within 2 months after surgery in approximately 30%. There were no significant

differences in adverse events and complications between the groups (Table 2). The median postoperative hospital stay and median days to diet initiation were 12 days (interquartile range [IQR], 7–17) and 4 days (IQR, 3–6) in the ONS group and 11 days (IQR, 7–19) and 3 days (IQR, 2–5) in the control group.

The primary outcome, %BWL, was significantly prevented in the ONS group (−4.8% vs. −6.4%, $P = 0.039$) in the ITT analysis, and essentially the same result was obtained in the PPS analysis (sensitivity analysis) (−4.7% vs. −6.4%, $P = 0.036$). Subgroup analyses also showed a consistent trend toward reduced %BWL in the ONS group across most subgroups. The effect was more pronounced in patients who underwent TG (MD: 5.0%, 95% CI: −2.3, 12.30, $P = 0.151$) and those with low BMI (MD: 2.3%, 95% CI: −0.4, 5.0, $P = 0.088$), although these differences were not statistically significant (Supplementary Table 1, Supplemental Digital Content 1, <http://links.lww.com/SLA/F584>).

Handgrip strength and hematologic and blood chemistry were not significantly different between the two groups at postoperative 8 weeks (Table 3). However, the ONS group maintained handgrip strength in the subgroup with low handgrip strength (−0.9% vs. −9.7%, MD: 8.8, 95% confidence interval [CI]: −4.9, 22.5, $P = 0.193$), although the difference was not significant (Supplementary Table 2, Supplemental Digital Content 1, <http://links.lww.com/SLA/F584>).

The detailed information on HRQoL scores in each group at baseline and 8 weeks after surgery are shown in Supplementary Table 3, Supplemental Digital Content 1, <http://links.lww.com/SLA/F584>. Figure 2 shows the baseline-adjusted HRQoL at 8 weeks after surgery. Insomnia (MD: 9.88, 95% CI: 3.18, 16.58, $P = 0.004$), appetite loss (MD: 10.97, 95% CI: 0.63, 21.31, $P = 0.038$), and diarrhea (MD: 9.80, 95% CI: 0.38, 19.21, $P = 0.042$) were worse in the ONS group, but the other functions and symptoms were similar between the two groups, as shown by the EORTC QLQ scores. However, the proportion of patients with severe symptoms, defined as ≥ 66 scores at postoperative 8 weeks, were not significantly different between the groups (insomnia: 8% vs. 12%, $P = 0.523$; appetite loss: 15% vs. 28%, $P = 0.069$; and diarrhea: 15% vs. 10%, $P = 0.428$). The postoperative mean EuroQol-5D-5L utility scores of the control group and ONS group were similar (0.91 vs. 0.90, MD: -0.01 , 95% CI: -0.52 , 0.03 , $P = 0.662$). Dietary intake data standardized by body weight are shown in Table 4. The baseline data between the groups were similar. At postoperative 8 weeks, carbohydrate in dietary intake other than ONS was lower in the ONS group than in the control group (2.5 vs. 3.0 g/kg, $P = 0.022$). However, the data, including the ONS nutrients, showed that the total caloric intake (23.1 vs. 21.6 kcal/kg, $P = 0.111$) and carbohydrate intake (3.6 vs. 3.0 g/kg, $P = 0.072$) were higher in the ONS group than in

the control group, although the differences were not significant. Protein intake also was significantly higher in the ONS group than in the control group (1.0 vs. 0.8 g/kg, $P = 0.006$).

The average number of days to start ONS after surgery was 7.1 ± 1.5 days. A total of 56 (93%) and 47 (78%) patients continued to record an ONS diary at least until 7 weeks and 8 weeks after surgery, respectively. Four patients discontinued diary recording within 6 weeks after surgery. Missing diary entries were treated as zero intake, and the average daily ONS intake was calculated. The estimated adherence data for each patient is presented in Figure 3. The average ONS intake was at least 308.7 ± 97.0 mL per day, with at least 51 (85%) patients consuming 200 mL or more of ONS daily. Although additional nutritional supplementation was permitted for the control group, only 2 patients received it: one consumed 350 mL of a polymeric formula, and another consumed 400 mL of a nonpolymeric ONS. In a post-intervention questionnaire ($n = 57$), 77.2% of patients reported a favorable taste of the ONS, while 14.0% reported taste-related issues, and 8.8% reported gastrointestinal symptoms as reasons for non-adherence.

DISCUSSION

This RCT evaluated the efficacy of a simple ONS, mainly containing carbohydrate and protein, on BWL, muscle strength, and HRQoL in patients undergoing gastrectomy for GC. The simple

ONS led to lower postoperative BWL in the ONS group than in the control group by offering good palatability and adherence due to its uncomplicated composition. Although the ONS group had low carbohydrate intake, the addition of ONS nutrients resulted in higher total intake of calories, carbohydrates, and protein. These findings highlight the potential of simple ONS to prevent postoperative nutritional decline, which is a critical concern in patients undergoing gastrectomy.

A recent systematic review concluded that ONS interventions could improve BWL in patients with GC after gastrectomy.²⁸ Although some studies have demonstrated the potential benefits of ONS, variability in ONS adherence rates (45%–68%) may have contributed to inconsistent clinical benefit.^{4–8} The taste, texture, and flavor are vital determinants of ONS adherence, which can be negatively affected by ONS nutrients, such as fat, vitamins, minerals, and amino acids.¹⁰ To improve adherence, we used a simple ONS formulation, which might contribute to higher adherence, with >75% of patients reporting that the taste of the ONS was favorable.

In principle, to effectively prevent postoperative BWL, invasive procedures must be minimized, including avoidance of TG. The KEGG group has helped develop evidence supporting minimally invasive gastrectomy including robotic surgery.^{29–35} Our cohort included

fewer open (2%) as well as total gastrectomies (8%) and a higher proportion of robotic surgeries (60%) than in previous studies, which aligns with recent surgical practice.^{36–38} We still demonstrated a significant reduction in BWL with ONS administration. The mean difference in BWL between the ONS and control groups after distal gastrectomy was 1.3%, which is greater than the 0.5% reported by Imamura et al., possibly due to better adherence (309 vs. 200 kcal/day).

In addition to taste and texture, patient instructions are crucial in achieving high ONS adherence. Meng et al. reported a significant effect of ONS on %BWL after gastrectomy and emphasized the importance of patient education, including biweekly telephone follow-ups.¹³ Our study incorporated several strategies to promote adherence, including in-hospital monitoring and follow-up review of ONS diaries.¹⁴

A previous study that failed to demonstrate the benefit of ONS after gastrectomy reported that ONS might suppress food intake,⁶ nevertheless, a few studies have examined the details and extent of dietary intake.^{5,7,25} Our findings showed that the total intake of calories, protein, and carbohydrates was higher in the ONS group than in the control group. These findings will be informative for patients and medical workers. Furthermore, medical workers

should advise patients that although ONS may suppress their food intake, it increases their total energy intake.

The ONS used in this study contained 10 g of whey protein, including branched-chain amino acids, per 200 mL. Although the intervention increased the protein intake, it did not improve the handgrip strength of all participants; nevertheless, the potential benefit of ONS on handgrip strength was observed in patients with low baseline handgrip strength, consistent with the results of a recent study focusing on malnourished patients.¹¹ Future studies are warranted to evaluate the potential benefits of ONSs on muscle strength.

Regarding HRQoL, the ONS group showed statistically worse scores for insomnia, appetite loss, and diarrhea on the QLQ-C30. The observed differences (approximately 10 points) in these symptoms may not be negligible,³⁹ although most were mild; only one patient used antidiarrheal agents, and no patients required sleeping medication. The cause of increased insomnia remains unclear; however, gastrointestinal discomfort secondary to ONS use may have interfered with sleep. These findings highlight the need to monitor patient-reported outcomes and provide guidance on ONS intake timing and speed. Future studies should qualitatively explore this relationship.

Although the 1.7% difference in BWL between the two groups (−4.8% vs. −6.4%) at 2 months after surgery was statistically significant, its clinical relevance remains unclear. A relationship between postoperative BWL and prognosis has been reported,⁴⁰ and preventing BWL in the early postoperative period may enhance body image, alleviate anxiety, and reduce long-term BWL. Moreover, the greater effects observed in subgroups, including patients with low BMI or those who underwent TG, suggest that the clinical significance may be even greater in these high-risk populations. Future studies should further explore the clinical significance of early postoperative BWL.

This study had several limitations. First, we did not compare other types of ONS products, although the simplicity of ONS may have contributed to good adherence, which is a strength of this study. It was difficult to determine how the ONS product's simplicity affected the findings of less BWL and good adherence. Second, the dietary intake and ONS adherence data relied on self-reported information; nevertheless, these data were confirmed by the dietitian or the investigator with patients in their outpatient visits, leading to more reliable and less missing data. Third, this study was conducted across Japanese hospitals belonging to the KEGG group, which may affect the generalizability of the study results. Although our clinical

pathway is largely consistent with international standards, the reproducibility of these results should be carefully considered in other countries.

In conclusion, the reduction in postoperative BWL in patients with GC after gastrectomy was significantly higher in the ONS group than in the control group with a regular diet administered for 8 weeks.

DECLARATIONS

Authors' Contributions

All authors contributed to the conception and conduct of this clinical trial. KO is the principal investigator of this trial. KU and NT designed the overall framework of the trial, and AN was responsible for the statistical design to test efficacy. KU and TN drafted the manuscript. All authors helped refine the final manuscript and approved it.

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Figure 1. Consort flow diagram.

Figure 1. CONSORT flow diagram

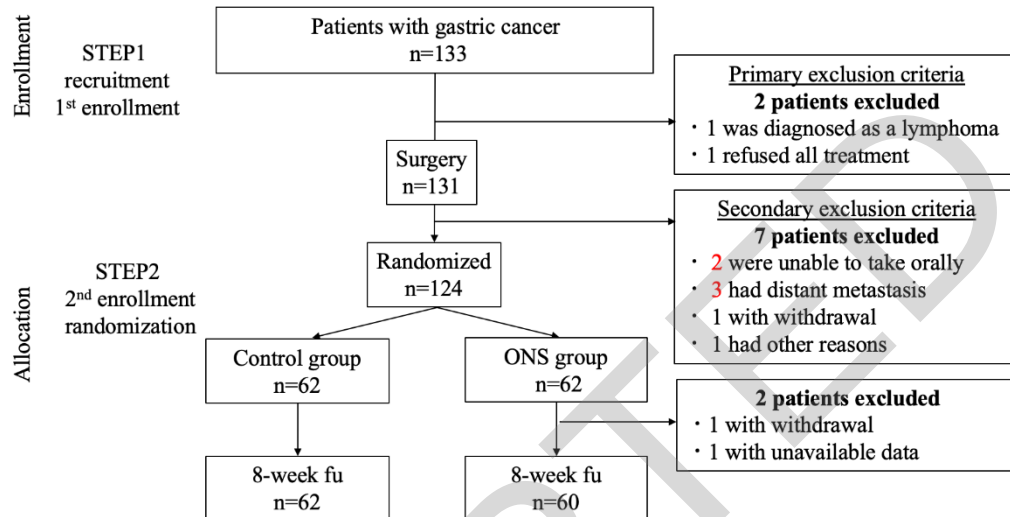


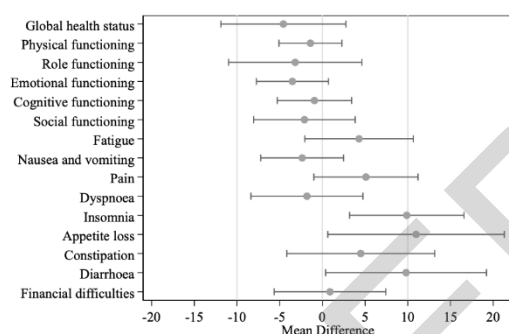
Figure 2. Comparison of baseline-adjusted HRQoL scores at 8weeks postoperatively scores in

(A) the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and

(B) EORTC QLQ-OG25.

Figure 2. Comparison of baseline-adjusted HRQoL scores at 8weeks postoperatively in (A) EORTC QLQ-C30 and (B) EORTC QLQ-OG25

(A) EORTC QLQ-C30



(B) EORTC QLQ-OG25

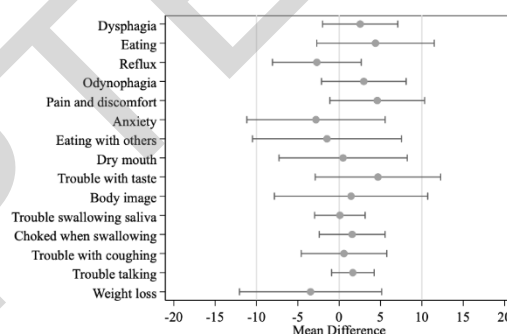


Figure 3. Average amount of oral nutritional supplement (ONS) intake for each patient.

Figure 3. Average amount ONS intake for each patient

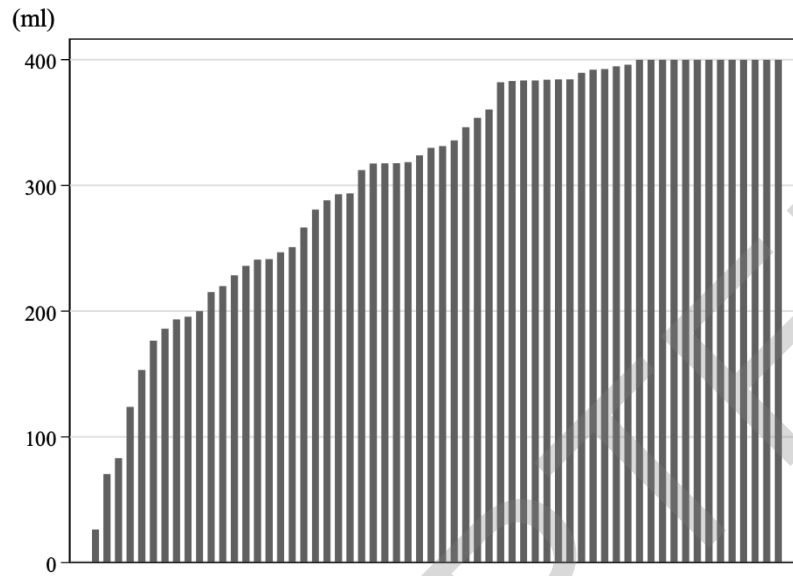


Table 1. Baseline demographic and pathological characteristics

		Control group (n=62)	ONS group (n=60)	P value
Sex, male		37 (59.7%)	35 (58.3%)	0.881
Age, years		68 (11)	67 (11)	0.531
Weight, kg (at baseline)		60.1 (10.8)	59.3 (11.4)	0.709
BMI, kg/m ²		22.7 (2.9)	22.3 (3.6)	0.457
ASA-PS	1	26 (41.9%)	16 (26.7%)	0.148
	2	35 (56.5%)	41 (68.3%)	
	3	1 (1.6%)	3 (5.0%)	
Charlson Comorbidity Score (at baseline)		3.6 (1.6)	3.6 (1.6)	0.966
Histological type	Differentiated	35 (56.5%)	25 (41.7%)	0.102
	Undifferentiated	27 (43.5%)	35 (58.3%)	
Clinical Stage	I	40 (64.5%)	35 (58.3%)	0.483
	≥II	22 (35.5%)	25 (41.7%)	
Handgrip strength, kg (at baseline)		30.1 (8.4)	29.6 (8.6)	0.763
Low handgrip strength, yes		9 (15%)	12 (20%)	0.422
Hemoglobin, g/dl (at baseline)		12.8 (2.0)	12.5 (1.9)	0.443
Lymphocyte, /m ³ (at baseline)		1766.8 (642.2)	1676.1 (500.8)	0.39
Albumin, g/dl (at baseline)		4.0 (0.3)	4.1 (0.4)	0.843
PNI (at baseline)		49.2 (4.7)	49.0 (5.1)	0.782
Pathological Stage	I	32 (51.6%)	28 (46.7%)	0.585
	≥II	30 (48.4%)	32 (53.3%)	
Type of gastrectomy	Distal gastrectomy	51 (82.3%)	53 (88.3%)	0.704
	Billroth I	25 (49%)	24 (45.3%)	
	Billroth II	9 (17.6%)	12 (22.6%)	
	Roux-en-Y	17 (33.3%)	17 (32.1%)	
	Proximal gastrectomy	2 (3.2%)	2 (3.3%)	
	Total gastrectomy	6 (9.7%)	4 (6.7%)	
	Pylorus-preserving gastrectomy	3 (4.8%)	1 (1.7%)	
Operative approach	Laparoscopic	24 (38.7%)	25 (41.7%)	0.944
	Robotic	37 (59.7%)	34 (56.7%)	
	Open	1 (1.6%)	1 (1.7%)	
Adjuvant chemotherapy, yes		15 (24.2%)	19 (31.7%)	0.357

Data are shown as the number of patients (%) or the mean (standard deviation). BMI, Body Mass Index; ASA-PS, American Society of Anesthesiologists-Physical status; ECOG-PS, Eastern Cooperative Oncology Group-performance Status; PNI, Prognostic Nutritional Index; ONS, oral nutritional supplements.

Table 2. Details of Adverse Events and Complications

	Control group (n=62)	ONS group (n=60)	P value
All adverse events (Grade2)	7 (11%)	4 (7%)	0.373
Anastomotic leak	1	0	
Pancreatic fistula	1	0	
Abdominal abscess	1	0	
Ileus	1	0	
Diarrhea	0	1	
Vomiting	1	1	
Elevated serum liver enzyme level	1	1	
Others	3	3	

CTCAE v5.0 was used to evaluate the severity. ONS, oral nutritional supplements.

Table 3. Comparison of Primary and Secondary Outcomes

	Control group (n=62)	ONS group (n=60)	Mean difference (95% confidence interval)	P value
Body weight loss, %	-6.4	-4.8	1.7 (0.1, 3.2)	0.039
Handgrip strength at 8weeks postoperatively, kg	29.1	28.2	-0.9 (-3.9, 2.2)	0.572
Change in handgrip strength, %	-3.5	-4.1	-0.69 (-4.0, 2.6)	0.683
Hemoglobin at 8weeks postoperatively, g/dl	12.1	12.0	-0.1 (-0.6, 0.4)	0.589
Lymphocyte at 8weeks postoperatively, /m3	1847.3	1706.9	-140.4 (-367.6, 86.8)	0.223
Albumin at 8weeks postoperatively, g/dl	4.0	4.0	0.0	0.841

One missing data in lymphocyte at baseline and at 8week postoperatively for one case, respectively.

ONS, oral nutritional supplements.

Table 4. Analysis of Dietary Intake Data

		Control group	ONS group		
		N=41	N=49		
	Dietary intake	Dietary intake	P value	Including ONS	P value
Preoperative baseline					
Energy intake, kcal/kg	23.9 (19.3-31.3)	26.4 (21.8-30.6)	0.283	-	-
Carbohydrate, g/kg	3.6 (2.8-4.5)	3.6 (2.8-4.2)	0.551	-	-
Protein, g/kg	0.9 (0.7-1.2)	1.0 (0.8-1.2)	0.196	-	-
Fat, g/kg	0.7 (0.5-1.0)	0.8 (0.6-1.1)	0.079	-	-
At 8 weeks after surgery					
Energy intake, kcal/kg	21.6 (15.8-25.9)	17.9 (13.7-25.2)	0.182	23.1 (20.1-29.9)	0.111
Carbohydrate, g/kg	3.0 (2.4-4.0)	2.5 (1.8-3.5)	0.022	3.6 (3.1-4.5)	0.072
Protein, g/kg	0.8 (0.5-1.1)	0.7 (0.6-1.0)	0.633	1.0 (0.8-1.2)	0.006
Fat, g/kg	0.6 (0.4-0.8)	0.6 (0.4-0.8)	0.920	-	-

Data was shown as median (interquartile). There is missing data (n=1) in each group at 8 weeks after surgery. Each P value was calculated compared with control group. ONS, oral nutritional supplements.