ANTICANCER RESEARCH *46*: 4523-4534 (2026)
doi: 10.21873/anticanres.18308

Long-term Outcomes of OGSG1108: A Supplemental Study of Oral Nutritional Supplementation During Adjuvant S-1 Chemotherapy

YOSHITOMO YANAGIMOTO[1,2], TOSHIMASA TSUJINAKA[3], JUNJI KAWADA[4], MASAAKI MOTOORI[5], JIN MATSUYAMA[6], HIROSHI IMAMURA[2], RYOHEI KAWABATA[7], KENTARO INOUE[8], SHUGO UEDA[9], KOICHI DEMURA[10], ATSUSHI TAKENO[11], OSAMU TAKAYAMA[12], KENICHI NAGAI[13], SHINICHI ADACHI[14], TAKESHI OMORI[1], YUKINORI KUROKAWA[15], SHUNJI ENDO[16], TOSHIO SHIMOKAWA[17] and TAROH SATOH[18]; OSAKA GASTROINTESTINAL CANCER CHEMOTHERAPY STUDY GROUP (OGSG)

[1]Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan;
[2]Department of Surgery, Toyonaka Municipal Hospital, Osaka, Japan;
[3]Department of Gastroenterological Surgery, Izumi City General Hospital, Osaka, Japan;
[4]Department of Gastroenterological Surgery, Nippon Life Hospital, Osaka, Japan;
[5]Department of Gastroenterological Surgery, Osaka General Medical Center, Osaka, Japan;
[6]Department of Gastroenterological Surgery, Higashiosaka City Medical Center, Osaka, Japan;
[7]Department of Gastroenterological Surgery, Sakai City Medical Center, Osaka, Japan;
[8]Department of Gastroenterological Surgery, Kansai Medical University, Osaka, Japan;
[9]Department of Gastroenterological Surgery, Kitano Hospital, Osaka, Japan;
[10]Department of Gastroenterological Surgery, Japan Community Health Care Organization Osaka Hospital, Osaka, Japan;
[11]Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan;
[12]Department of Surgery, Kaizuka City Hospital, Osaka, Japan;
[13]Department of Surgery, Hoshigaoka Medical Center, Osaka, Japan;
[14]Department of Gastroenterological Surgery, Nishinomiya Municipal Central Hospital, Hyogo, Japan;
[15]Department of Gastroenterological Surgery, The University of Osaka Graduate School of Medicine, Osaka, Japan;
[16]Department of Gastroenterological Surgery, Kawasaki Medical School Hospital, Okayama, Japan;
[17]Department of Biostatistics, Faculty of Medicine, Wakayama Medical University, Wakayama, Japan;
[18]Center for Cancer Genomics and Precision Medicine, The University of Osaka Graduate School of Medicine, Osaka, Japan

Abstract

Background/Aim: The OGSG1108 trial evaluated the effect of oral elemental nutritional supplementation (ONS) on one-year compliance with adjuvant S-1 chemotherapy after gastrectomy for pathological stage II/III gastric cancer. It remains unknown whether intervention with ONS affords survival benefits, along with enhanced compliance with adjuvant chemotherapy.

Patients and Methods: Two groups of patients registered in the OGSG1108 trial were compared. The on-protocol group included 81 patients with pathological stage II/III gastric cancer and good acceptability (≥60%) in an ONS compliance

continued

Yoshitomo Yanagimoto, MD, PhD, Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan. Tel: +81 669451181, Fax: +81 669451908, e-mail: yoshitomo-0225@outlook.com

Received May 7, 2026 | Revised May 27, 2026 | Accepted May 28, 2026

test, who were eligible for the second registration and received protocol-based treatment with adjuvant S-1 and ONS. The off-protocol group included 24 patients with pathological stage II/III gastric cancer and poor acceptability (<60%) in an ONS compliance test, who were ineligible for the second registration and received optional adjuvant S-1 as an off-protocol treatment. Supplemental data were collected for both groups. Patient characteristics, biochemical and oncological factors, postoperative complications, number of S-1 chemotherapy courses, overall survival (OS), and relapse-free survival (RFS) were compared and prognostic factors were analyzed.

Results: The number of S-1 courses was comparable between the two groups (on-protocol *vs.* off-protocol: 6.3±2.5 *vs.* 5.9±3.3). No significant differences were observed in 5-year OS (71.9% *vs.* 66.7%, p=0.700) or RFS (58.4% *vs.* 62.5%, p=0.972). A multivariate analysis identified pathological stage and number of S-1 courses as independent prognostic factors, but not acceptability of ONS.

Conclusion: Postoperative intervention with ONS did not seem to improve the prognosis of patients receiving adjuvant S-1 treatment. The number of S-1 courses was a prognostic factor.

Keywords: Gastric cancer, gastrectomy, oral nutritional supplementation, adjuvant chemotherapy, long-term effects.

Introduction

Although age-adjusted incidence and mortality rates are declining, gastric cancer remains the fifth most commonly diagnosed malignancy and the fourth leading cause of cancer-related deaths globally (1). Although surgical resection is the main curative modality for gastric cancer, postoperative body weight loss (BWL) is frequently observed and considered unavoidable in most patients. This phenomenon is attributable to several factors, including a hypercatabolic state induced by surgery-related inflammatory responses, an impaired oral intake and nutrient absorption due to the loss of gastric reservoir capacity, and reduced secretion of gastric acid and pancreatic enzymes (2, 3). Depending on the extent of resection, BWL at one year postoperatively has been reported to range from 6% to 18% (4-7).

Several small-scale randomized controlled trials (RCTs) have reported that oral elemental nutritional supplementation (ONS) after gastrectomy prevents BWL (8-10). In contrast, large-scale RCTs have failed to show a significant effect of ONS in attenuating BWL after gastrectomy (11, 12). Therefore, the necessity of unexceptional intervention with ONS in patients after gastrectomy has been questioned (13, 14).

Postoperative adjuvant chemotherapy with oral fluoropyrimidines after gastrectomy with D2 lymphadenectomy is widely accepted as the standard treatment for advanced gastric cancer in East Asia. Previous studies have demonstrated that the intensity and continuity of adjuvant chemotherapy are critical determinants of the long-term prognosis (15-19). BWL was proven to compromise both dose intensity and compliance with adjuvant chemotherapy, leading to worse clinical outcomes after curative surgery for gastric cancer (20).

A multicenter, open-label, single-arm phase II clinical trial (OGSG1108) was conducted to prove that ONS would not only mitigate BWL but also improve compliance with adjuvant S-1 chemotherapy in patients with gastric cancer. In the OGSG1108 trial, ONS was administered for six months in combination with postoperative adjuvant S-1 chemotherapy for patients with pathological stage II or III gastric cancer, and favorable results were obtained with a 1-year S-1 completion rate of 69.0% and a relative performance (RP) rate of 87.5% (21), which exceeded the expected threshold level. Survival data were not collected, and only patients with good acceptability of ONS showing no recurrence within one year were evaluated.

This supplemental study was designed to confirm the hypothesis that ONS not only enhances compliance with

adjuvant chemotherapy but also improves survival. We extracted two groups with pathological stage II/III gastric cancer from patients registered in the OGSG1108 trial: the on-protocol group showed good acceptance of ONS and received protocol-based treatment with S-1 and ONS; the off-protocol group showed poor acceptance of ONS and received optional adjuvant S-1 as an off-protocol treatment. Supplemental data were collected and comparisons between the two groups were performed.

Patients and Methods

OGSG1108. OGSG1108 was a multicenter, open-label, single-arm phase II trial conducted by the Osaka Gastrointestinal Cancer Chemotherapy Study Group between February 2012 and July 2014, employing a two-step registration process. Patients eligible for the first registration had gastric adenocarcinoma treated with curative distal or total gastrectomy, an Eastern Cooperative Oncology Group performance status (PS) of 0-2, clinical stage II or III disease, and an adequate postoperative oral intake to permit ONS administration. The ONS compliance test was conducted during the period between surgery and the initiation of adjuvant S-1 chemotherapy. Patients received an ONS at a dose of 300 kcal/day for at least 14 days. Patients who consumed ≥60% of the planned dose were considered compliant and were eligible for the second registration. For the second registration, patients were required to have pathological stage II or III disease based on the third English edition of the Japanese Classification of Gastric Carcinoma (22) and ≥60% acceptability of a planned dose of ONS (Elental® 300 kcal/day; EA Pharma Co., Ltd., Tokyo, Japan) for a planned duration of at least 14 days in the ONS compliance test performed before starting adjuvant chemotherapy. After applying the eligibility criteria of the ACTS-GC phase III trial, which evaluated the efficacy of adjuvant S-1 chemotherapy in patients with pathological stage II or III gastric cancer, patients with pathological T1N+ or T3N0 disease were excluded from the study (23). S-1 (80 to 120 mg per day) was given for four weeks, followed by two weeks of rest. This 6-week cycle was repeated for one year. Elental® is an elemental diet containing a high proportion of L-glutamine, designed to support nutritional intake in patients with a compromised gastrointestinal function. Consequently, as an orally administrable formulation in which essential amino acids serve as the sole nitrogen source and fat content is minimized, it is expected to reduce the risk of malabsorption and gastrointestinal intolerance. Patients enrolled in the second registration were strictly controlled to receive adjuvant S-1 chemotherapy for one year in association with ONS for six months and optionally extended to one year. The primary endpoint was the S-1 completion rate, defined as the proportion of patients who entered the second registration and continued eight consecutive courses of S-1 for one year with an RP (administered/planned S-1doses ×100%) value of ≥70%.

Study design and patient groups. This supplemental study was planned in May 2024 and approved by the institutional review boards of all hospitals participating in the OGSG1108 trial. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Toyonaka Municipal Hospital (approval number: 2023-08-05). The requirement for written informed consent was waived owing to the retrospective nature of the study. A CONSORT diagram for this study is shown in Figure 1. A total of 149 patients were initially enrolled at the first registration, and 121 patients had ≥60% acceptance of the planned dose of ONS in the ONS compliance test. After the exclusion of 40 patients (nine with pathological stage I, 10 with pathological T1N+ or T3N0 disease, 20 did not meet the eligibility criteria for the second registration, and one had synchronous or metachronous multiple cancers), 81 patients with pathological stage II excluding T1N+ or T3N0 or III were consequently eligible for the second registration and received protocol-based adjuvant chemotherapy with S-1 along with ONS (on-protocol group). Twenty-eight patients with <60% acceptance of ONS were ineligible for the second registration. After excluding four patients (one with pathological stage I, one with pathological T1N+ or T3N0 disease, and two with

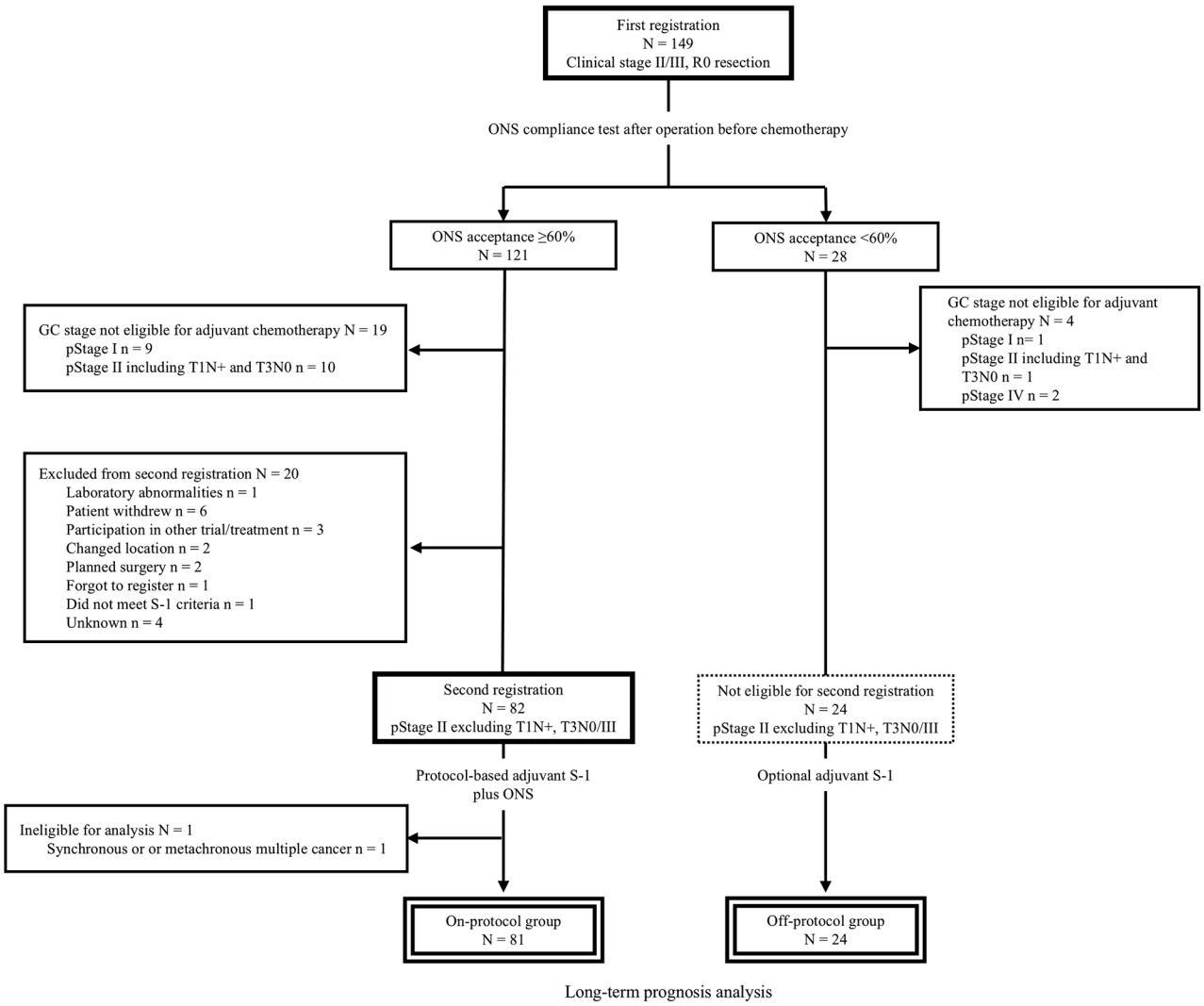

Figure 1. *CONSORT diagram. At the first registration, 149 gastric cancer patients with R0 resection, PS 0-2, clinical stage II or III disease, and adequate postoperative oral intake were enrolled. In the oral elemental nutritional supplementation (ONS) compliance test, acceptability of a planned dose of ONS for a planned duration of at least 14 days was evaluated. Among 121 patients with ≥60% acceptability of the planned ONS dose in the ONS compliance test, 40 patients were excluded because of pathological stage I disease (n=9), pathological T1N+ or T3N0 disease (n=10), failure to meet the eligibility criteria for the second registration (n=20), or synchronous/metachronous multiple cancers (n=1). Consequently, 81 patients with pathological stage II or III disease were received protocol-based adjuvant chemotherapy with S-1 along with ONS (on-protocol group). Among twenty-eight patients with <60% acceptability of the planned ONS, four patients were excluded because of pathological stage I disease (n=1), pathological T1N+ or T3N0 disease (n=1), or pathological stage IV disease (n=2). Consequently, 24 patients with pathological stage II or III disease received optional adjuvant S-1 chemotherapy (off-protocol group). GC: Gastric cancer.*

pathological stage IV), 24 patients with pathological stage II, excluding T1N+ or T3N0 or III, received optional adjuvant S-1 chemotherapy (off-protocol group).

Supplemental data were collected for these two groups to obtain overall survival (OS), relapse-free survival (RFS), postoperative complications according to the Clavien–Dindo classification, number of postoperative S-1 chemotherapy courses, and data on patient background characteristics (age, sex, PS, and body mass index), blood biochemical parameters, Glasgow Prognostic Score (GPS),

oncological factors (histological type, T and N classification, and pathological stage), and acceptability of ONS in the ONS compliance test.

Statistical analyses. OS was defined as the time from the date of surgery to death due to any cause. RFS was defined as the time from surgery to first recurrence or death in the absence of recurrence. Survival curves for OS and RFS were estimated using the Kaplan–Meier method and compared between the on-protocol and off-protocol groups using the log-rank test. Continuous variables are reported as the mean±standard deviation or median with range, whereas categorical variables are expressed as percentages with corresponding 95% confidence intervals (CIs). The χ^2 test was used to assess differences in categorical data, and Student's *t*-test was used to compare continuous variables between groups. Multivariate analyses were performed using a Cox proportional hazards model with backward stepwise selection to identify factors associated with OS and RFS. In the multivariable analysis, postoperative infectious complications were included as a covariate because infectious events (*e.g.,* anastomotic leakage, pancreatic fistula, and intra-abdominal abscess) have been reported as significant adverse prognostic factors after gastrectomy (24, 25). *p*-Values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed using R (ver. 4.4.2, the R Foundation for Statistical Computing, Vienna, Austria).

Results

Background of patient groups. The clinicopathological characteristics of the patients are summarized in Table I. The following background data were comparable between the off-protocol and on-protocol groups: age, 69 *vs*. 70 years; PS 0, 11 (45.8%) *vs*. 43 (53.1%); PS 1, 13 (54.2%) *vs*. 38 (46.9%); median body mass index (BMI), 23.0 (15.5-31.3) *vs*. 20.8 (13.4-29.0), pathological stage (pStage) II, 9 (37.5%) *vs*. 27 (33.3%); pStage III, 15 (62.5%) *vs*. 54 (66.7%); GPS 0, 16 (66.7%) *vs*. 62 (76.5%); GPS 1/2, 8 (33.3%) *vs*. 19 (23.5%). Regarding surgical procedures, total and distal gastrectomy were performed in nine (37.5%) and 15 (62.5%) patients, respectively, in the off-protocol group and in 26 (32.1%) and 55 (67.9%) patients in the on-protocol group. Postoperatively, there was a significantly higher incidence of severe complications (Clavien–Dindo grade ≥3a) in the off-protocol group (6/24, 25.0%; $p<0.001$) than in the on-protocol group (1/81, 1.2%). The ONS compliance test revealed marked differences in the acceptability of ONS between the two groups. In the Off-protocol group, ONS intake per day relative to the planned dose was 20% for 14 days, in contrast to 100% for 18 days in the on-protocol group. As shown in Table II, the baseline laboratory values of the two groups were comparable.

Postoperative adjuvant chemotherapy and prognosis. The number of postoperative adjuvant chemotherapy courses administered is shown in Figure 2. The mean number of courses administered was 5.9±3.3 in the off-protocol group and 6.3±2.5 in the on-protocol group. In the off-protocol group, three patients (12.5%) did not receive any postoperative adjuvant chemotherapy. The number of patients who completed all eight courses of postoperative adjuvant chemotherapy was 15 (62.5%) in the off-protocol group and 47 (58.0%) in the on-protocol group. Among the patients who experienced Clavien–Dindo grade ≥3a postoperative complications, three of the six patients in the off-protocol group completed all eight courses of adjuvant S-1 chemotherapy, one completed seven courses, one completed six courses, and one did not receive any adjuvant chemotherapy. In the on-protocol group, a single patient with a complication discontinued the adjuvant chemotherapy during the first course.

Figure 3 shows the RFS and OS curves. The median RFS was 97.7 [54.8-not available (NA)] months in the off-protocol group and 87.8 (53.6-NA) months in the on-protocol group. The 3- and 5-year RFS rates were 66.7% and 62.5%, respectively, in the off-protocol group and 63.6% and 58.4% in the on-protocol group [hazard ratio (HR)=0.99; 95%CI=0.52-1.89, $p=0.972$]. The median OS was 113.8 (61.1-NA) months in the off-protocol group and

Table I. *Patient characteristics.*

	Off-protocol Group (n=24)	On-protocol Group (n=81)
Age, years; median [range]	69 [35-89]	70 [42-85]
Sex; number (%)		
Male	15 (62.5)	49 (60.5)
Female	9 (37.5)	32 (39.5)
ECOG PS; number (%)		
0	11 (45.8)	43 (53.1)
1	13 (54.2)	38 (46.9)
BMI, kg/m^2; median [range]	23.0 [15.5-31.3]	20.8 [13.4-29.0]
Type of gastrectomy; number (%)		
Total	9 (37.5)	26 (32.1)
Distal	15 (62.5)	55 (67.9)
Histology; number (%)		
Intestinal	13 (54.2)	37 (45.7)
Diffuse	11 (45.8)	43(53.1)
Mixed	0	1(1.2)
pStage; number (%)		
IIA	3 (12.5)	9 (11.1)
IIB	6 (25.0)	18 (22.2)
IIIA	5 (20.8)	23 (28.4)
IIIB	6 (25.0)	14 (17.3)
IIIC	4 (16.7)	17 (21.0)
GPS score; number (%)		
0	16 (66.7)	62 (76.5)
1	6 (25.0)	16 (19.8)
2	2 (8.3)	3 (3.7)
Postoperative complication ≥C-D grade 3a; number (%)		
Pancreatic fistula	3 (12.5)	0
Abdominal abscess	4 (16.7)	0
leakage	1 (4.2)	1 (1.2)
Stenosis	2 (8.3)	0
Bleeding	0	0
Pneumonia	0	0
Ileus	0	0
Acceptability at the ONS compliance test		
Duration of ONS intake (day); median [range]	14 [7, 21]	18 [13, 21]
ONS intake per day compared to planned dose (%); median [range]	20 [0, 100]	100 [60, 100]

BMI: Body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; GPS: Glasgow Prognostic Score; C-D: Clavien-Dindo classification; ONS: oral nutritional supplement.

127.0 (86.1-NA) months in the on-protocol group. The 3- and 5-year OS rates were 75.0% and 66.7%, respectively, in the off-protocol group and 78.4% and 71.9% in the on-protocol group (HR=0.87; 95%CI=0.44-1.73, p=0.700).

Multivariate analyses of prognostic factors. The multivariate analysis of factors associated with RFS revealed that pathological stage (HR=2.02; 95%CI=1.06-3.85, p=0.033) and the number of adjuvant chemotherapy courses (HR=3.04; 95%CI=1.58-5.85, p<0.001) were independent risk factors. Likewise, the multivariate analysis of factors associated with OS revealed that pathological stage (HR=2.68; 95%CI=1.34-5.39, p=0.006) and the number of adjuvant chemotherapy courses (HR=2.27; 95%CI=1.11-4.66, p=0.025) were independent risk factors (Table III).

Discussion

We evaluated the long-term outcomes of patients enrolled in the OGSG1108 trial to investigate the effect of ONS on

Table II. *Baseline laboratory values of the two groups.*

Laboratory parameter	Off-protocol Group (n=24)	On-protocol Group (n=81)
WBC (/μl)	6,960 [3,800-11,890]	5,400 [2,900-11,480]
Neutrophils (/μl)	3,755.5 [1,684-10,938]	3,010 [422-7,310]
Platelets ($\times 10^4$/μl)	28.5 [14.8-48.1]	23.4 [9.3-56.5]
Hemoglobin (g/dl)	11.4 [7.5-15.4]	11.8 [8.2-15.6]
AST (U/l)	24 [12-49]	24 [11-268]
ALT (U/l)	20 [12-89]	21 [7-158]
Creatinine (mg/dl)	0.70 [0.37-1.06]	0.73 [0.40-1.13]
Total bilirubin (mg/dl)	0.5 [0.3-1.1]	0.5 [0.2-0.9]
CRP (mg/dl)	0.14 [0-11.23]	0.13 [0.01-4.04]
Albumin (g/dl)	3.9 [1.7-4.6]	3.9 [2.5-4.7]
Total protein (g/dl)	6.7 [5.4-7.5]	6.8 [5.7-8.7]
Total cholesterol (mg/dl)	180 [126-203]	160 [101-211]

Data expressed as median [range]. WBC: White blood cell count; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

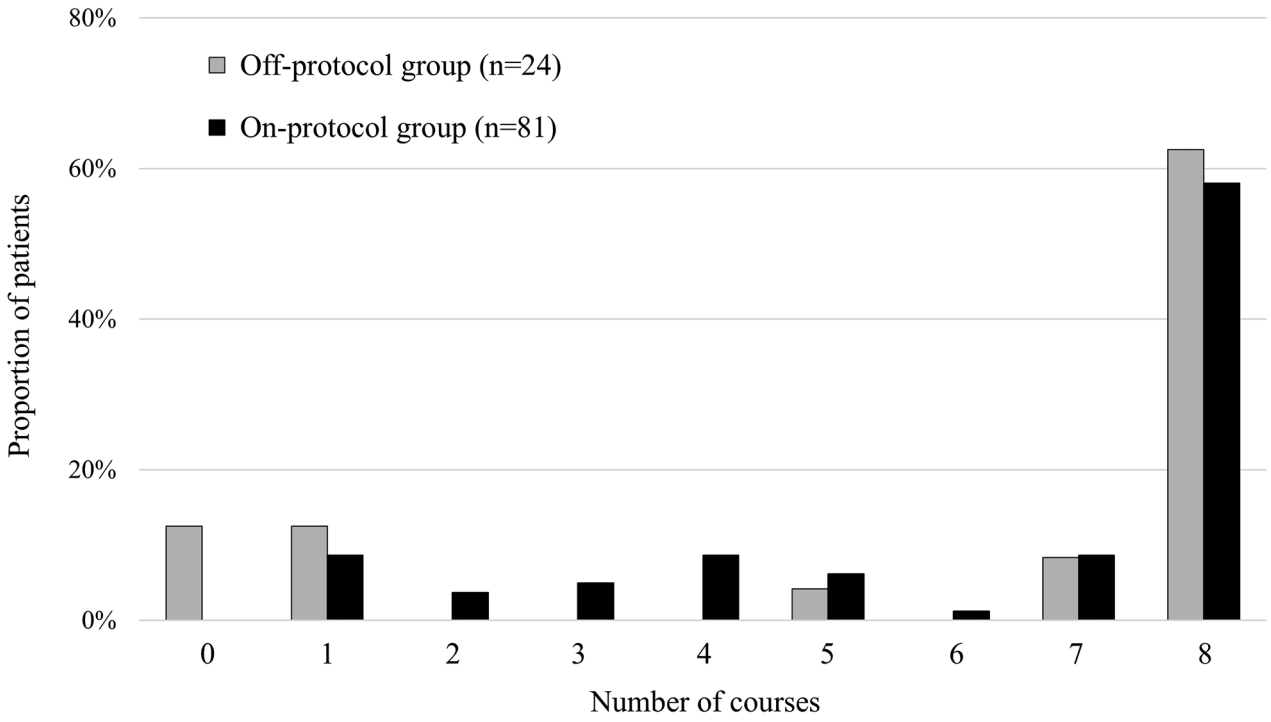

Figure 2. *Number of courses of adjuvant S-1 chemotherapy. The graph shows the proportion of patients according to the number of administered adjuvant S-1 courses in each group (gray bars: off-protocol group; black bars: on-protocol group).*

the long-term prognosis of patients with pathological stage II/III gastric cancer receiving adjuvant S-1 chemotherapy. There were no significant differences in RFS or OS between the on-protocol and off-protocol groups, indicating that active ONS did not affect the prognosis of these patients. Multivariate analyses identified pathological stage and number of adjuvant chemotherapy courses as independent prognostic factors,

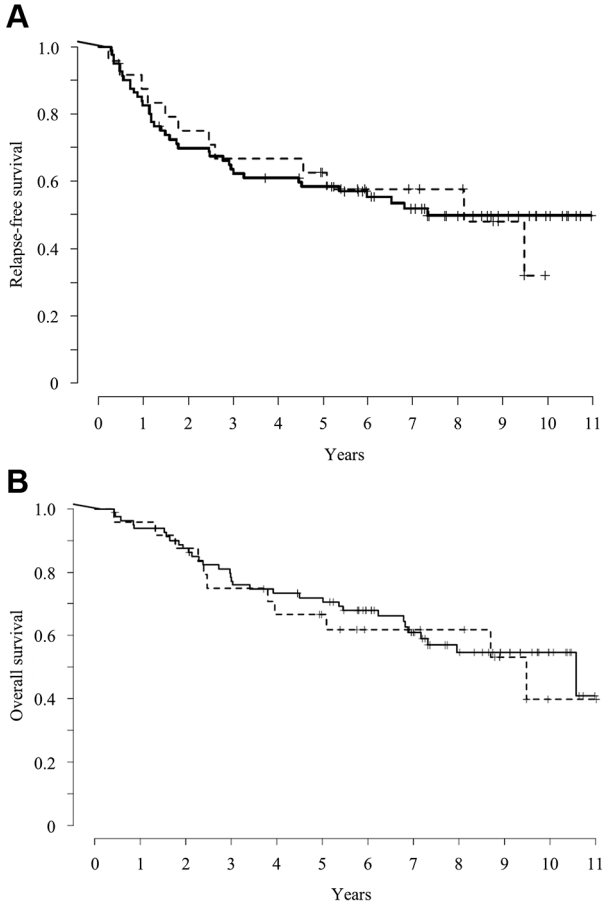

Figure 3. *Survival data. A) Relapse-free survival of the off-protocol (dashed line) and on-protocol (solid line) groups. B) Overall survival of the off-protocol (dashed line) and on-protocol (solid line) groups.*

whereas the acceptability of ONS was not identified as a prognostic factor.

The relationship between dose intensity of adjuvant S-1 chemotherapy and long-term survival has been reported in previous studies (26, 27). Notably, in a large-scale phase III RCT (OPAS-1), patients with pathological stage II disease assigned to receive eight courses of S-1 had significantly better survival outcomes than those assigned to receive four courses (28). In this study, we compared the intensity of postoperative S-1 chemotherapy by estimating the number of administered courses and completion rate of patients assigned to receive eight courses; however, no differences were found between the two groups, which may indicate the absence of significant differences in survival.

Previously, RCTs were conducted to evaluate the effects of perioperative nutritional interventions in patients with gastric cancer, focusing on BWL as a primary endpoint. One RCT was designed to confirm the preventive effect of ONS (ProSure®; Abbott Japan, Tokyo, Japan) at a dose of 600 kcal per day during the perioperative period (1-7 days before surgery and 2-21 days after surgery) on BWL after total gastrectomy. However, it failed to demonstrate the superiority of EPA (eicosapentaenoic acid) administration over a standard diet alone (12). The supplemental study reported survival of the two groups as a key secondary endpoint, disclosing no survival benefit in the intervention group, while the pathological stages of enrolled patients and details of adjuvant chemotherapy were not available (29). Another RCT aimed to assess the efficacy of postoperative administration of ONS (Racol® NF; Otsuka Pharmaceutical Factory, Tokyo, Japan) for patients with gastric cancer, initiated within three days after the resumption of oral intake at 400 kcal/day for a duration of three months (11), which revealed that the administration of ONS did not improve BWL at one year after gastrectomy. As a supplemental analysis, the induction and continuation rates at three months of adjuvant chemotherapy along with survival outcomes were compared between groups with various pathological stages and mixed chemotherapeutic regimens (30). ONS failed to show any notable benefit in survival in comparison to no intervention, and subgroup analyses could not detect any specific patient population in which ONS conferred a survival advantage. The findings of these two trials are consistent with the results of the present study, which focused on a homogeneous cohort of patients with pathological stage II/III disease and evaluated the actual cycles of adjuvant S-1. This approach enabled us to demonstrate that the prognosis was associated with the intensity of adjuvant S-1 treatment rather than with ONS. Taken together, regardless of ONS regimens and intervention periods, postoperative nutritional intervention with ONS did not seem to improve long-term

Table III. *Multivariate and backward stepwise analyses of prognostic factors for relapse-free and overall survival.*

	Relapse-free survival				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR [95%CI]	*p*-Value	HR [95%CI]	*p*-Value	HR [95%CI]	*p*-Value	HR [95%CIs]	*p*-Value
Age (<70/≥70 years)	1.646 [0.813, 3.333]	0.166		-	1.383 [0.642, 2.977]	0.407		-
Sex (Male/Female)	0.944 [0.454, 1.963]	0.878		-	0.823 [0.383, 1.770]	0.618		-
pStage (II/III)	2.482 [1.202, 5.126]	0.014	2.020 [1.059, 3.853]	0.033	2.944 [1.376, 6.298]	0.005	2.684 [1.336-5.391]	0.006
GPS score (0/1, 2)	0.723 [0.294, 1.778]	0.479		-	0.595 [0.230, 1.541]	0.285		-
Type of gastrectomy (Distal/Total)	0.887 [0.412, 1.911]	0.76		-	1.068 [0.452, 2.523]	0.881		-
Acceptability of ONS (<80/≥80%)*	0.825 [0.290, 2.344]	0.718		-	0.898 [0.318, 2.537]	0.838		-
Number of courses of adjuvant S-1 chemotherapy (≥5/≤4 courses)	3.054 [1.491, 6,258]	0.002	3.037 [1.577, 5.848]	<0.001	2.135 [0.984, 4.629]	0.055	2.272 [1.107-4.662]	0.025
Postoperative infectious complications (present/absent)	0.555 [0.0531, 5.800]	0.623		-	0.931 [0.0844, 10.27]	0.954		-

GPS: Glasgow Prognostic Score; ONS: oral nutritional supplement. *Cutoff point was set at the middle of 60 to 100 based on the results of the ONS compliance test.

outcomes in patients with gastric cancer, although it does not deny the importance of nutritional management for patients after gastrectomy.

Postoperative complications (PCs) have been reported to induce poor adherence to adjuvant chemotherapy and unfavorable long-term outcomes after gastrectomy (31). In the present study, a higher incidence of PCs was observed in the off-protocol group than in the on-protocol group, but there were no differences in the cycles of adjuvant chemotherapy and survival data. PCs might affect acceptance of ONS within a short period after surgery due to delayed intestinal recovery, while the negative effect of PCs might be attenuated after sufficient postoperative recovery when adjuvant S-1 chemotherapy is generally initiated. In addition, the multivariate analysis did not show that PC was a prognostic factor. Given the small number of major complication events and the limited statistical power in this study, this finding should be interpreted with caution. However, further investigations are warranted to determine the relationship between PCs and compliance with adjuvant chemotherapy and the long-term prognosis.

Study limitations. First, as it was conducted as a supplemental analysis, postoperative adjuvant chemotherapy was evaluated based solely on the number of courses administered, and the actual dose intensity could not be calculated. Second, postoperative body weight data were unavailable for the off-protocol group, rendering it impossible to evaluate differences in BWL between the groups. Consequently, the relationship between BWL and long-term outcomes remains unclear. Third, the sample size of this study was not large enough to avoid a type II error, although survival data were well established because the follow-up period exceeded 10 years. Fourth, in this study, oral nutritional intake from regular meals (excluding ONS) was not quantitatively assessed, and standardized nutritional counseling or support by dietitians was not provided. Therefore, the potential influence of overall dietary intake on the study outcomes could not be evaluated.

Conclusion

In this supplemental study, we were unable to demonstrate a clear prognostic benefit of postoperative ONS in patients with gastric cancer receiving adjuvant S-1 chemotherapy after gastrectomy. In contrast, cycles of adjuvant S-1 chemotherapy were significantly associated with improved long-term outcomes.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Y.Y., H.Im. and T.T. designed this study. Y.Y., J.K., M.M., J.M., H.Im., R.K., K.I., S.U., K.D., A.T., O.T., K.Na., S.A., T.O., H.Ik. and K.Ni. contributed to patient enrollment and data collection. T.S. performed statistical analyses. T.T. supervised the study. S.E. provided critical review and guidance on the manuscript. All Authors reviewed and approved the final version of the manuscript.

Acknowledgements

The Authors would like to express their sincere gratitude to the members of the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) for their valuable contributions to patient enrollment, data collection, and study coordination.

Funding

This research received no external funding.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

References

1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F: Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71(3): 209-249, 2021. DOI: 10.3322/caac.21660

2 Friess H, Böhm J, Müller MW, Glasbrenner B, Riepl RL, Malfertheiner P, Büchler MW: Maldigestion after total gastrectomy is associated with pancreatic insufficiency. Am J Gastroenterol 91(2): 341-347, 1996.

3 Brägelmann R, Armbrecht U, Rosemeyer D, Schneider B, Zilly W, Stockbrügger RW: Nutrient malassimilation following total gastrectomy. Scand J Gastroenterol Suppl 31(sup218): 26-33, 1996. DOI: 10.3109/00365529609094727

4 Davis JL, Selby LV, Chou JF, Schattner M, Ilson DH, Capanu M, Brennan MF, Coit DG, Strong VE: Patterns and predictors of weight loss after gastrectomy for cancer. Ann Surg Oncol 23(5): 1639-1645, 2016. DOI: 10.1245/s10434-015-5065-3

5 Hirao M, Takiguchi S, Imamura H, Yamamoto K, Kurokawa Y, Fujita J, Kobayashi K, Kimura Y, Mori M, Doki Y, Osaka University Clinical Research Group for Gastroenterological Study: Comparison of Billroth I and Roux-en-Y reconstruction after distal gastrectomy for gastric cancer: one-year postoperative effects assessed by a multi-institutional RCT. Ann Surg Oncol 20(5): 1591-1597, 2013. DOI: 10.1245/s10434-012-2704-9

6 Masuzawa T, Takiguchi S, Hirao M, Imamura H, Kimura Y, Fujita J, Miyashiro I, Tamura S, Hiratsuka M, Kobayashi K, Fujiwara Y, Mori M, Doki Y: Comparison of perioperative and long-term outcomes of total and proximal gastrectomy for early gastric cancer: a multi-institutional retrospective study. World J Surg 38(5): 1100-1106, 2014. DOI: 10.1007/s00268-013-2370-5

7 Kurokawa Y, Sasako M, Sano T, Shibata T, Ito S, Nashimoto A, Kurita A, Kinoshita T, Japan Clinical Oncology Group: Functional outcomes after extended surgery for gastric cancer. Br J Surg 98(2): 239-245, 2011. DOI: 10.1002/bjs.7297

8 Feijó PM, Rodrigues VD, Viana MS, Dos Santos MP, Abdelhay E, Viola JP, De Pinho NB, Martucci RB: Effects of ω-3 supplementation on the nutritional status, immune, and inflammatory profiles of gastric cancer patients: A randomized controlled trial. Nutrition 61: 125-131, 2019. DOI: 10.1016/j.nut.2018.11.014

9 Meng Q, Tan S, Jiang Y, Han J, Xi Q, Zhuang Q, Wu G: Post-discharge oral nutritional supplements with dietary advice in patients at nutritional risk after surgery for gastric cancer: A randomized clinical trial. Clin Nutr 40(1): 40-46, 2021. DOI: 10.1016/j.clnu.2020.04.043

10 Imamura H, Nishikawa K, Kishi K, Inoue K, Matsuyama J, Akamaru Y, Kimura Y, Tamura S, Kawabata R, Kawada J, Fujiwara Y, Kawase T, Fukui J, Takagi M, Takeno A, Shimokawa T: Effects of an oral elemental nutritional supplement on

post-gastrectomy body weight loss in gastric cancer patients: a randomized controlled clinical trial. Ann Surg Oncol 23(9): 2928-2935, 2016. DOI: 10.1245/s10434-016-5221-4

11 Miyazaki Y, Omori T, Fujitani K, Fujita J, Kawabata R, Imamura H, Okada K, Moon J, Hirao M, Matsuyama J, Saito T, Takahashi T, Kurokawa Y, Yamasaki M, Takiguchi S, Mori M, Doki Y, Osaka University Clinical Research Group for Gastroenterological Study: Oral nutritional supplements versus a regular diet alone for body weight loss after gastrectomy: a phase 3, multicenter, open-label randomized controlled trial. Gastric Cancer 24(5): 1150-1159, 2021. DOI: 10.1007/s10120-021-01188-3

12 Ida S, Hiki N, Cho H, Sakamaki K, Ito S, Fujitani K, Takiguchi N, Kawashima Y, Nishikawa K, Sasako M, Aoyama T, Honda M, Sato T, Nunobe S, Yoshikawa T: Randomized clinical trial comparing standard diet with perioperative oral immunonutrition in total gastrectomy for gastric cancer. Br J Surg 104(4): 377-383, 2017. DOI: 10.1002/bjs.10417

13 Kikuchi S, Takata N, Kakiuchi Y, Kuroda S, Kashima H, Tanabe S, Noma K, Takahashi A, Kagawa S, Fujiwara T: Effect of oral nutritional supplements composed of high protein on body weight loss after gastrectomy. In Vivo 39(1): 426-432, 2025. DOI: 10.21873/invivo.13845

14 Furuta R, Hatao F, Itokawa M, Yamazaki R, Morikawa Y, Honda M, Imamura K, Ishibashi Y, Morita Y: Feasibility and safety of super energy-dense oral nutritional supplementation in postoperative gastric cancer patients. Cancer Diagn Progn 3(4): 514-521, 2023. DOI: 10.21873/cdp.10248

15 Yamamoto M, Omori T, Shinno N, Hara H, Mukai Y, Sugase T, Takeoka T, Mikamori M, Kanemura T, Hasegawa S, Akita H, Haraguchi N, Nishimura J, Wada H, Matsuda C, Yasui M, Miyata H, Ohue M: Adjuvant chemotherapy with S-1 plus docetaxel versus S-1 plus oxaliplatin in stage III gastric cancer. Anticancer Res 43(11): 5015-5024, 2023. DOI: 10.21873/anticanres.16700

16 Mita K, Ito H, Ota E, Takahashi K, Hashimoto M, Asakawa H, Hayashi T, Fujino K: Adjuvant chemotherapy with S-1 plus cisplatin for patients with stage III gastric cancer after curative resection. Anticancer Res 37(3): 1329-1334, 2017. DOI: 10.21873/anticanres.11451

17 Noh SH, Park SR, Yang HK, Chung HC, Chung IJ, Kim SW, Kim HH, Choi JH, Kim HK, Yu W, Lee JI, Shin DB, Ji J, Chen JS, Lim Y, Ha S, Bang YJ, CLASSIC trial investigators: Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. Lancet Oncol 15(12): 1389-1396, 2014. DOI: 10.1016/s1470-2045(14)70473-5

18 Park SH, Lim DH, Sohn TS, Lee J, Zang DY, Kim ST, Kang JH, Oh SY, Hwang IG, Ji JH, Shin DB, Yu JI, Kim KM, An JY, Choi MG, Lee JH, Kim S, Hong JY, Park JO, Park YS, Lim HY, Bae JM, Kang WK, ARTIST 2 investigators: A randomized phase III trial comparing adjuvant single-agent S1, S-1 with oxaliplatin, and postoperative chemoradiation with S-1 and oxaliplatin in patients with node-positive gastric cancer after D2 resection: the ARTIST 2 trial☆. Ann Oncol 32(3): 368-374, 2021. DOI: 10.1016/j.annonc.2020.11.017

19 Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y: Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 *versus* surgery alone in stage II or III gastric cancer. J Clin Oncol 29(33): 4387-4393, 2011. DOI: 10.1200/jco.2011.36.5908

20 Aoyama T, Yoshikawa T, Shirai J, Hayashi T, Yamada T, Tsuchida K, Hasegawa S, Cho H, Yukawa N, Oshima T, Rino Y, Masuda M, Tsuburaya A: Body weight loss after surgery is an independent risk factor for continuation of S-1 adjuvant chemotherapy for gastric cancer. Ann Surg Oncol 20(6): 2000-2006, 2013. DOI: 10.1245/s10434-012-2776-6

21 Imamura H, Matsuyama J, Nishikawa K, Endo S, Kawase T, Kimura Y, Fukui J, Kawada J, Kurokawa Y, Fujitani K, Sakai D, Kawakami H, Tsujinaka T, Shimokawa T, Matsubara Y, Satoh T, Furukawa H, Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG): Effects of an oral elemental nutritional supplement in gastric cancer patients with adjuvant S-1 chemotherapy after gastrectomy: A multicenter, open-label, single-arm, prospective phase II study (OGSG1108). Ann Gastroenterol Surg 5(6): 776-784, 2021. DOI: 10.1002/ags3.12487

22 Japanese Gastric Cancer Association: Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 14(2): 101-112, 2011. DOI: 10.1007/s10120-011-0041-5

23 Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 357(18): 1810-1820, 2007. DOI: 10.1056/nejmoa072252

24 Fujiya K, Tokunaga M, Mori K, Makuuchi R, Tanizawa Y, Bando E, Kawamura T, Terashima M: Long-term survival in patients with postoperative intra-abdominal infectious complications after curative gastrectomy for gastric cancer: a propensity score matching analysis. Ann Surg Oncol 23(S5): 809-816, 2016. DOI: 10.1245/s10434-016-5577-5

25 Tokunaga M, Tanizawa Y, Bando E, Kawamura T, Terashima M: Poor survival rate in patients with postoperative intra-abdominal infectious complications following curative gastrectomy for gastric cancer. Ann Surg Oncol 20(5): 1575-1583, 2013. DOI: 10.1245/s10434-012-2720-9

26 Miyatani K, Saito H, Shimizu S, Kono Y, Murakami Y, Shishido Y, Matsunaga T, Fukumoto Y, Fujiwara Y: Late start and insufficient S-1 dose in adjuvant chemotherapy can lead to poor prognosis in stage II/III gastric cancer. Int J Clin Oncol 24(10): 1190-1196, 2019. DOI: 10.1007/s10147-019-01468-0

27 Nishibeppu K, Komatsu S, Kosuga T, Kubota T, Okamoto K, Konishi H, Shiozaki A, Fujiwara H, Otsuji E: Cumulative total S-1 dose in adjuvant chemotherapy affects the long-term outcome following curative gastrectomy for gastric cancer. Am J Cancer Res 11(5): 2312-2318, 2021.

28 Yoshikawa T, Terashima M, Mizusawa J, Nunobe S, Nishida Y, Yamada T, Kaji M, Fukushima N, Hato S, Choda Y, Yabusaki H, Yoshida K, Ito S, Takeno A, Yasuda T, Kawachi Y, Katayama H, Fukuda H, Boku N, Sano T, Sasako M: Four courses versus eight courses of adjuvant S-1 for patients with stage II gastric cancer (JCOG1104 [OPAS-1]): an open-label, phase 3, non-inferiority, randomised trial. Lancet Gastroenterol Hepatol 4(3): 208-216, 2019. DOI: 10.1016/s2468-1253(18)30383-2

29 Aoyama T, Yoshikawa T, Ida S, Cho H, Sakamaki K, Ito Y, Fujitani K, Takiguchi N, Kawashima Y, Nishikawa K, Nunobe S, Hiki N: Effects of perioperative eicosapentaenoic acid-enriched oral nutritional supplement on the long-term oncological outcomes after total gastrectomy for gastric cancer. Oncol Lett 23(5): 151, 2022. DOI: 10.3892/ol.2022.13272

30 Omori T, Yamamoto K, Kurokawa Y, Miyazaki Y, Fujitani K, Kawabata R, Imamura H, Takeno A, Yanagimoto Y, Takahashi T, Saito T, Eguchi H, Doki Y: Long-term effects of oral nutritional supplements after gastrectomy for gastric cancer: a survival analysis from a multicenter, open-label, randomized controlled trial. Ann Surg Oncol 31(10): 6909-6917, 2024. DOI: 10.1245/s10434-024-15667-1

31 Jin GY, Park KB, Song KY: Factors related to compliance with adjuvant chemotherapy in patients with gastric cancer: A retrospective single-center study. Korean J Clin Oncol 17(1): 31-36, 2021. DOI: 10.14216/kjco.21005