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Original article

Title

Long-term effects of oral nutritional supplements after gastrectomy for gastric cancer: a survival analysis from a multicenter, open-label, randomized controlled trial

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A short running head

ONS and prognosis in gastric cancer

Conflicts of interest

We declare that we have no conflicts of interest.

Synopsis

Oral nutritional supplements for 3 months after gastrectomy for gastric cancer demonstrated no improvement in compliance with adjuvant chemotherapy or survival outcomes.

Abstract

Background: Weight loss (WL) after gastrectomy for gastric cancer is associated with both decreased compliance with adjuvant chemotherapy and impaired survival. This study examined the effects of administering oral nutritional supplements (ONS) for 3 months after gastrectomy in terms of compliance with adjuvant chemotherapy and survival outcomes.

Methods: This large-scale, multicenter, open-label, randomized controlled trial enrolled 1,003 gastric cancer patients undergoing curative gastrectomy. Patients were assigned to the control group (n=503) or ONS group (n=500). In the ONS group, 400 kcal/day of ONS was recommended in addition to a regular diet for 3 months after gastrectomy. Compliance with adjuvant chemotherapy and survival outcomes were compared between the 2 groups.

Results: Compared with the control group, the ONS group showed significantly decreased WL at 3 months after gastrectomy (8.6±6.1 vs. 7.2±5.7%, respectively, P=0.0004). The control and ONS groups did not differ regarding the induction rate of adjuvant chemotherapy (84.9 vs. 82.8%, respectively, P=0.614) or the continuation rate at 3 months postoperatively (75.3 vs. 76.6%, respectively, P=0.809). ONS for 3 months showed no survival benefit; the 3- and 5-year overall survival (OS) rates were 91.3% and 87.6% in the control group and 89.6% and 86.4% in the ONS group, respectively, indicating no significant difference (P=0.548). Subgroup analysis could not detect a population in which ONS administration increased OS.

Conclusion: Administration of ONS for 3 months after gastrectomy was not associated with increased compliance with adjuvant chemotherapy or with improved prognosis.

Introduction

Gastric cancer is the fifth most common cancer worldwide, and the fourth leading cause of cancer deaths[1]. While curative gastrectomy is essential for the treatment of gastric cancer, weight loss (WL) remains one of the major complaints postoperatively [2]. WL is associated with not only a remarkable deterioration in quality of life[3], but also with reduced immune function[4] and worse prognosis due to decreased compliance with adjuvant chemotherapy[5,6].

WL after gastrectomy is known to be caused by the following factors: increased catabolism due to surgical stress and inflammation, decreased food storage capacity, malabsorption resulting from decreased pancreatic enzyme and gastric acid secretion, and decreased ghrelin secretion in the stomach[7-9]. Several surgical approaches have been used to reduce WL; these include procedures that avoid total gastrectomy as much as possible, such as subtotal gastrectomy with a very small remnant stomach[10,11] and minimally invasive surgery such as laparoscopic and robotic surgery[12 13,14]. However, the issue of WL after gastrectomy has not been resolved.

WL after gastrectomy is known to be time dependent, and is most pronounced during the first 3 months postoperatively. Overall, 10–20% of body weight was reported to be lost after gastrectomy; more than 80% of this WL was observed within the first 3 months postoperatively, while the remaining 20% occurred slowly over time[15].

The objective of the current study was to elucidate the long-term effects of ONS for 3 months after gastrectomy using the clinical data of patients who participated in a previously described large-scale (n=1,003), multicenter, open-label, randomized controlled trial that was conducted to evaluate the clinical impact of administering oral nutritional supplements (ONS) for 3 months after gastrectomy[16]. The results showed that WL at 3 months was significantly reduced in the ONS group than in the control group, but the difference became nonsignificant at 1 year postoperatively. However, the post-gastrectomy reduction of WL was maintained for up to 1 year in patients who received ≥200 kcal/day of ONS.

Methods

Study population and design

In this study, we examined patients enrolled in the Osaka University Clinical Research Group for Gastroenterological Study, a large-scale, multicenter, open-label, phase III randomized controlled trial at 22 hospitals, in which curative distal, proximal, and total gastrectomy (DG, PG, and TG, respectively) were performed between November 11, 2013, and July 13, 2017 for histologically proven primary gastric cancer. Details regarding the eligibility criteria and the 2-

stage enrollment system of the original trial have been reported previously[16]. The study protocol was approved by the institutional review board of each participating hospital before study initiation. This study was performed in accordance with both the Japanese Ethical Guidelines for Clinical Research and the international ethical recommendations documented in the Declaration of Helsinki. All patients provided written informed consent before randomization.

Surgical procedure

Patients underwent standard gastrectomy and lymph node dissection according to the Japanese Gastric Cancer Treatment Guidelines 2014 [17]. In most cases, D1 plus lymphadenectomy (D1 + dissection) was performed in patients with cT1 tumors without regional lymph node metastasis, while D2 lymphadenectomy was performed in patients with cT1 tumors with regional lymph node metastasis and in patients with cT2–4 tumors. The surgical approach (i.e., open or laparoscopic) and reconstruction method were not prescribed in the protocol, and depended on the gastric cancer treatment strategy at each institution. Surgical data and pathology results were recorded according to the 14th edition of the Japanese Classification of Gastric Carcinoma[18]. Postoperative management, including the resumption of oral intake other than ONS, was generally performed according to the clinical policies of each participating institution.

Intervention

As previously described, enrolled patients were randomly assigned (1:1) to either the ONS group or the control group, on the basis of stratification factors such as institution, disease stage, and type of gastrectomy. In addition to the regular diet, it was recommended that patients in the ONS group, but not the control group, receive 400 mL/day (400 kcal/day) of Racol NF for 3 months beginning within 3 days after resumption of the regular oral diet.

Postoperative adjuvant chemotherapy

Regarding postoperative adjuvant chemotherapy, oral administration of S-1 for 1 year was planned for patients with pathological stage II or III gastric cancer according to the Japanese Gastric Cancer Treatment Guidelines 2014 (ver. 4)[17,19]. Postoperative chemotherapy for stage III gastric cancer also included capecitabine plus oxaliplatin treatment for 6 months[20], or 6 months of S-1 plus docetaxel followed by 6 months of S-1[21]. In addition, intraperitoneal chemotherapy and other systematic chemotherapies were used depending on the policies and clinical trials of each participating institution [22].

Surveillance

The enrolled patients received surveillance at each institution's outpatient clinics on the

basis of the principles of the Japanese Gastric Cancer Treatment Guidelines 2014 (ver. 4)[17]. Surveillance included physical examinations and blood tests (such as serum albumin level, C-reactive protein (CRP) level, and levels of tumor markers including carcinoembryonic antigen and carbohydrate antigen 19-9) at 1 and 2 months postoperatively, then every 3 months for the first year postoperatively and every 6 months beyond the first year. Imaging tests such as computed tomography scans were recommended every 6 months until 5 years postoperatively.

Statistical analysis

Overall survival (OS) was defined as the period between surgery and death from any cause, and relapse-free survival (RFS) was defined as the period between surgery and recurrence, or between surgery and death if recurrence did not occur. OS and RFS curves were calculated using the Kaplan–Meier method, and were statistically compared between the ONS and control group using the log-rank test. Comparisons of OS curves between the 2 groups were examined according to each pathological stage. Additionally, for patients whose caloric intake of ONS was available from patient reports (n=403), the ONS group was divided into 2 subgroups: ≥200 kcal/day (based on half of the recommended amount of 400 kcal/day) versus <200 kcal/day. An analysis was performed to determine how OS was affected by the administration of ≥200 kcal/day of ONS. A subgroup analysis was performed with a proportional hazards model for OS

to evaluate the statistical interactions between the treatment groups and 7 prespecified subgroups. Continuous numerical data are expressed as the mean and standard deviation (SD), and the distribution of dichotomous data is presented as the percentage with the 95% confidence interval (CI). The χ^2 test was used to compare binary variables, and the Student t-test was used to compare continuous variables. All P values less than 0.05 were judged as statistically significant. Statistical analysis was performed using JMP software version 17.0.0 (SAS Institute, Cary, NC, USA). The trial is registered at the UMIN Clinical Trials Registry (UMIN=CTR) (UMIN000011919).

Results

Patient baseline characteristics

The Trial Consort Diagram was presented in a previous report[16]. Briefly, a total of 1,167 patients were enrolled in this study, and after the second-stage randomization and exclusion based on several criteria, 1,003 patients were randomly assigned to the 2 groups (503 to the control group and 500 to the ONS group) (Figure 1). The background characteristics of the patients in the 2 groups were well balanced, as described in Table 1.

Serum albumin level and WL at 3 months after gastrectomy

The mean serum albumin level and mean WL were compared between the 2 groups at 3 months after gastrectomy, because the ONS intervention period was 3 months. The mean serum albumin level was not significantly different between the ONS and control groups (4.02±0.36 vs. 3.99±0.38, respectively, P=0.181). By contrast, the mean WL in the ONS group was significantly reduced than that in the control group (7.2±5.7 vs. 8.6±6.1%, respectively, P=0.0004), although the difference was only 1.4%.

Postoperative adjuvant chemotherapy

Among patients with pathological stage IIA–IIIC (excluding T3N0 and T1N2–3) who received postoperative adjuvant chemotherapy, Table 2 compares the ONS and control groups in terms of induction rates and regimens, as well as continuation rates at 3, 6, and 12 months after gastrectomy. The treatment regimens were similar between the 2 groups. The ONS group, compared with the control group, did not have a higher induction rate (82.8 vs. 84.9%, respectively, P=0.614), or higher continuation rates at 3 months (76.6 vs. 75.3%, respectively, P=0.809), 6 months (66.9 vs. 66.4%, respectively, P=0.933), or 12 months (51.7 vs. 47.3%, respectively, P=0.446).

Prognosis

Full analysis set

Figure 2 shows RFS and OS curves. The 3- and 5-year OS rates were 91.3% and 87.6% in the control group and 89.6% and 86.4%% in the ONS group, respectively, with no significant differences between the 2 groups (hazard ratio 0.899, 95% CI 0.633–1.273, P=0.548). Figure 3 shows that there were no significant differences in OS curves between the control and ONS groups when stratified by pathological stage, and ONS administration was not associated with any survival benefit in more advanced cancers.

Effect of the administration of ≥200 kcal/day of ONS

Our previous report showed that the administration of ≥200 kcal/day of ONS suppressed WL for up to 1 year postoperatively. Therefore in this study we compared the OS of patients who consumed ≥200 kcal/day of ONS with the OS of patients who consumed <200 kcal/day of ONS and patients in the control group. The OS curve of the ≥200 kcal/day ONS group (n=221) did not differ from those of the <200 kcal/day ONS group (n=182) or the control group (n=503) (Figure 4). The 3- and 5-year OS rates of patients in the ≥200 kcal/day ONS group were 90.5% and 87.4%, respectively.

Subgroup analysis of OS

Subgroup analysis was performed with a proportional hazards model for OS to evaluate statistical interactions between treatment groups and backgrounds (Figure 5). The subgroups were defined on the basis of the following 7 factors: age, sex, BMI, serum albumin level, surgical approach, operative procedure, and pathological stage. There was no subgroup in which ONS administration was significantly associated with longer OS after gastrectomy.

Discussion

In this study, a survival analysis of data from a large RCT was performed to evaluate the effectiveness of ONS after gastric cancer surgery. The results showed that the administration of ONS for 3 months after surgery for gastric cancer did not affect compliance with adjuvant chemotherapy or prognosis.

Several retrospective analyses showed that postoperative WL was associated with both decreased compliance with adjuvant chemotherapy and impaired survival outcomes[23 5 6], and it has been hypothesized that gastric cancer treatment outcomes might improve if WL could be suppressed through perioperative nutritional support. An RCT examined the effects of eicosapentaenoic acid–rich ONS on prognosis after gastrectomy for gastric cancer[24]. No clear

survival benefit was observed, but the trial did not have a large enough sample size, and the primary endpoint, namely WL after gastrectomy, was not demonstrated in the trial[25]. The current study led to the same conclusion, namely the absence of a survival benefit of ONS in this setting. This study analyzed the data from the first RCT on this topic to be conducted with a sufficient sample size, and the first in which postoperative ONS administration was shown to be effective in suppressing postoperative WL[16]. Subgroup analyses in this study did not detect populations in which ONS was beneficial for OS after gastrectomy. The benefits of ONS were expected to be greater in patients with lower preoperative BMI, malnutrition, total gastrectomy (which is associated with higher WL), or more advanced disease for which postoperative chemotherapy is more important, but in fact ONS exhibited reduced benefits in these groups.

It has already been reported that preoperative nutritional supports in gastric cancer patients with severe malnutrition reduce postoperative surgical site infection. In this randomized controlled trial [26], there were only 26 patients (2.6%) (data not shown) of severe preoperative malnutrition that require nutritional support according to the ESPEN guidelines [27], and the details of preoperative nutritional supports were not investigated. Additionally, 63 out of 1003 enrolled patients received neoadjuvant chemotherapy, however neoadjuvant chemotherapy for advanced gastric cancer is now being actively employed in clinical trials and daily practice in Japan [22,28]. Therefore, preoperative nutritional supports with ONS for advanced gastric cancer

may reduce postoperative complications and improve prognosis than administering it postoperatively.

The EFFORT trial examined whether nutritional intervention improved disease outcomes and prognosis in patients with a variety of conditions not limited to gastric cancer[29]. While individualized nutritional support for medical patients at nutritional risk significantly reduced short-term mortality, there was no legacy effect on longer-term outcomes[30]. Together these results suggest that nutritional interventions for patients at nutritional risk, including those undergoing gastric cancer surgery, are effective during the interventions, but the effects will wane after the interventions are discontinued. Long-term interventions lasting several years, or other techniques that have not yet been developed, might be required to improve prognosis.

In terms of novel, alternative approaches, enforced enteral feeding and pharmacological interventions are possible candidates. Regarding enteral nutrition, in our study the difference in the mean WL rate with or without 3 months of ONS administration (average intake 208 kcal/day) was only about 1.4%. By contrast, in total gastrectomy patients reported by Komatsu et al., the difference after 3 months of nighttime home enteral nutrition (1,200 kcal/day) was quite large, at 11.2%, and this treatment significantly increased the compliance with postoperative adjuvant chemotherapy[31]. The enteral feeding tube were placed intraoperatively in only 9 patients (2 after total gastrectomy and 7 after distal gastrectomy, data not shown) in this study.

The large, sustained difference in WL caused by enforced enteral feeding might improve the prognosis of gastric cancer. One potential pharmacological intervention is ghrelin[32]. Ghrelin is a hormone secreted from the stomach that increases appetite and lean body weight[33 34]. Adachi et al. reported that ghrelin administration after total gastrectomy for gastric cancer significantly suppressed WL and lean body mass loss[35]. Anamorelin is an orally active ghrelin receptor agonist that can be used in Japan for cases of non–small cell lung cancer, gastric cancer, pancreatic cancer, and colorectal cancer that are accompanied by cachexia[36 37], but it cannot be used for WL after radical gastrectomy for gastric cancer. Expanding its indications remains a future challenge. Furthermore, since exercise therapy in addition to nutritional therapy may help to preserve or increase lean body mass from the previous report [2], so multimodal intervention including exercise therapy is possible candidate approach in the future trial.

This study had several limitations. First, the total nutritional intake in the ONS group was unclear, since the study did not assess caloric intake in the regular diet. Second, ONS administration was limited to 3 months, and ONS did not improve patients' nutritional status or reduce WL beyond 1 year after surgery. Third, the adjuvant chemotherapy continuation rate was compared between the 2 groups in the current study, however the ratio of chemotherapy dose to the total planned dose of adjuvant chemotherapy could not be compared due to detail of adjuvant chemotherapy were not recorded in case report form. Nevertheless, this study was part of a large,

multicenter RCT, and the survival analysis was conducted in a cohort that showed a significant reduction in WL after 3 months of ONS administration. In conclusion, ONS administration for 3 months after radical gastrectomy for gastric cancer significantly suppressed WL but did not lead to increased compliance with adjuvant chemotherapy or improved survival outcomes. Different approaches should be investigated in future prospective trials to identify nutritional interventions with larger, longer-lasting impacts on reducing WL after gastrectomy in gastric cancer patients.

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Author contributions

KY contributed to data interpretation and critical revision of the manuscript for important intellectual content. TO conducted data collection and wrote the initial draft of the manuscript. YK, YM, KF, RK, HI, AT, YY, TT, TS, HE, and YD contributed to data collection and interpretation and critical review of the manuscript. All authors read and approved the final version of the manuscript and have agreed to the accountability of all aspects of the study, thereby ensuring that any queries related to the accuracy or integrity of any part of the work are answerable.

Ethical Standards

All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent for study inclusion, or the equivalent, was obtained from all patients.

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Figure 1. CONSORT flow diagram

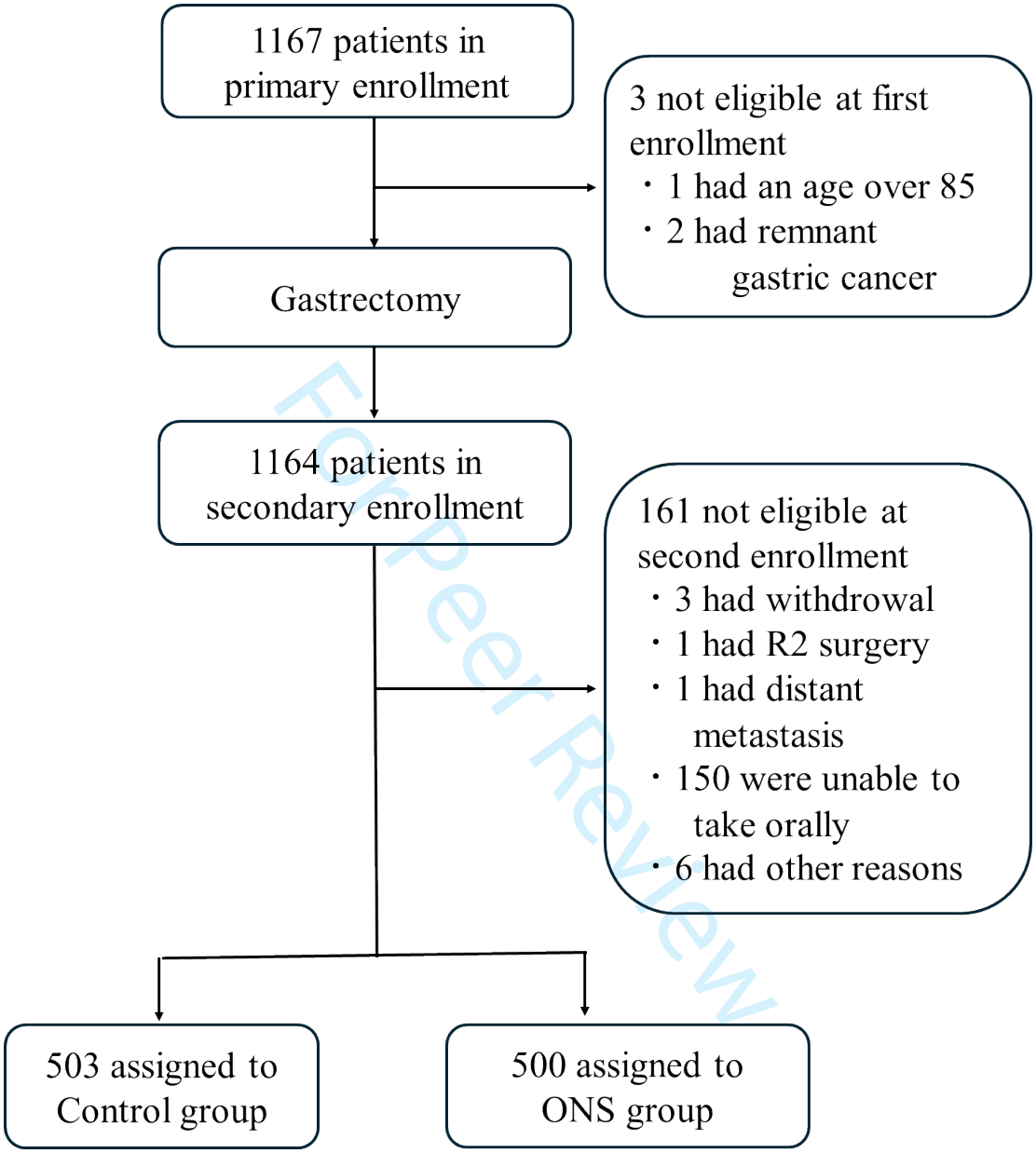
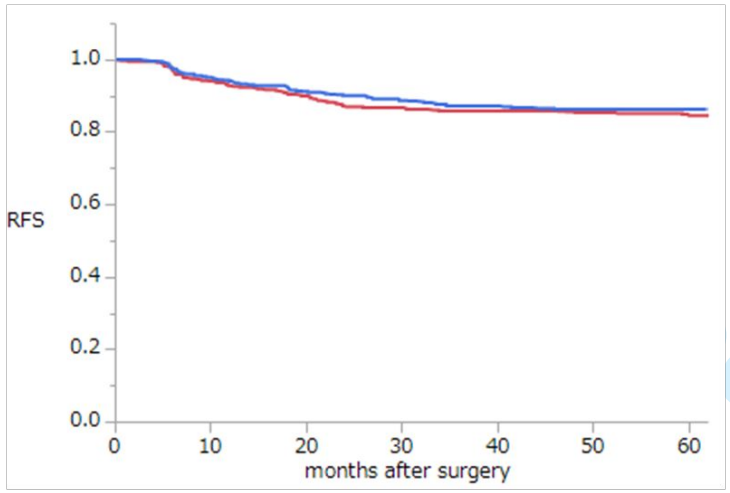


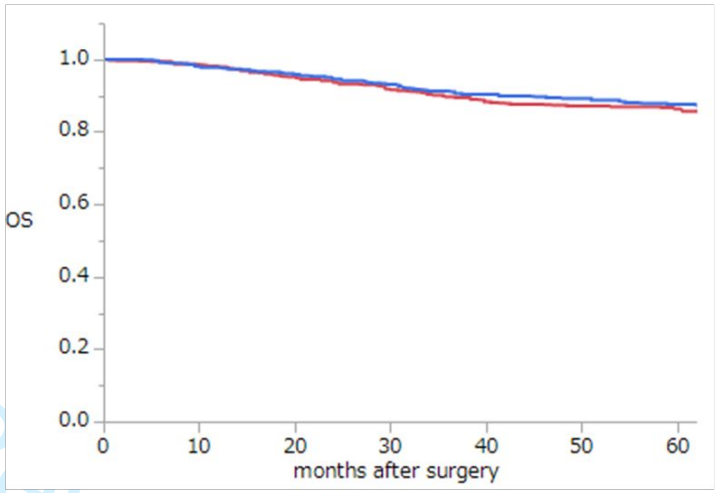
Figure 2. Survival

a)



Number at risk							
Control group	503	481	452	424	399	382	323
ONS group	500	472	442	416	388	371	313

b)



Number at risk							
Control group	503	463	423	399	382	367	313
ONS group	500	448	419	391	372	359	304

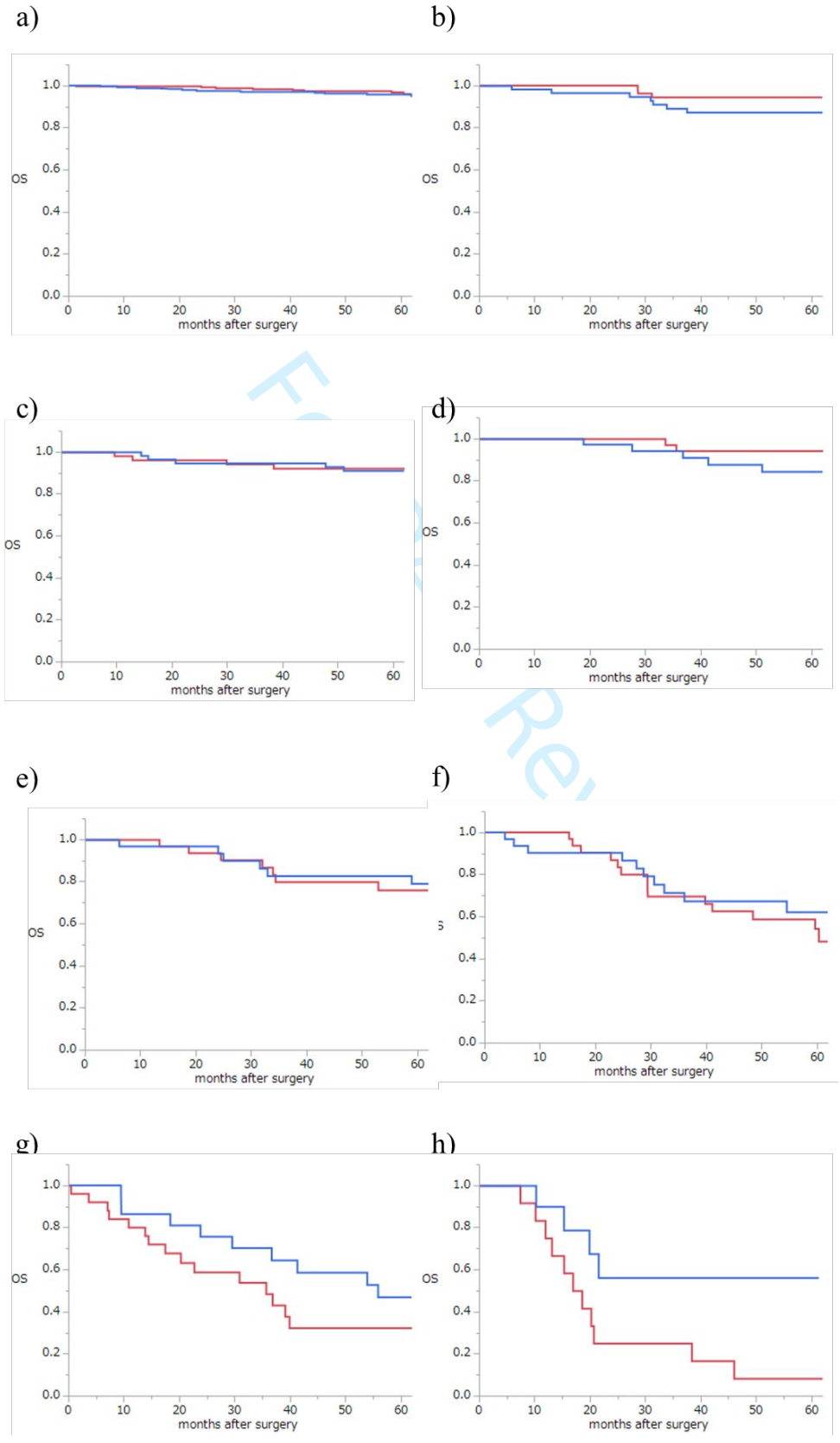
a) Relapse-free survival of the control group (n=503; blue line) and ONS group (n=500; red line)

b) Overall survival of the control group (n=503; blue line) and ONS group (n=500; red line)

RFS, relapse-free survival

OS, overall survival

Figure 3. OS curves after surgery by pathological stage

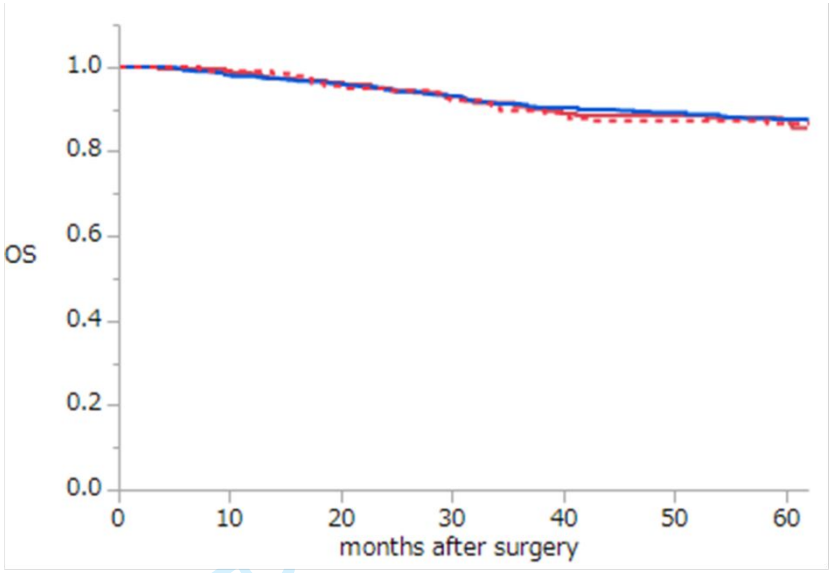


OS curve of the control group (blue line) and ONS group (red line)

a) OS curve of the control group (n=242) and ONS group (n=239) in stage IA (P=0.665)
b) OS curve of the control group (n=60) and ONS group (n=58) in stage IB (P=0.208)
c) OS curve of the control group (n=62) and ONS group (n=57) in stage IIA (P=0.899)
d) OS curve of the control group (n=37) and ONS group (n=37) in stage IIB (P=0.191)
e) OS curve of the control group (n=33) and ONS group (n=35) in stage IIIA (P=0.802)
f) OS curve of the control group (n=34) and ONS group (n=36) in stage IIIB (P=0.682)
g) OS curve of the control group (n=25) and ONS group (n=26) in stage IIIIC (P=0.174)
h) OS curve of the control group (n=10) and ONS group (n=12) in stage IV (P=0.056)

OS, overall survival

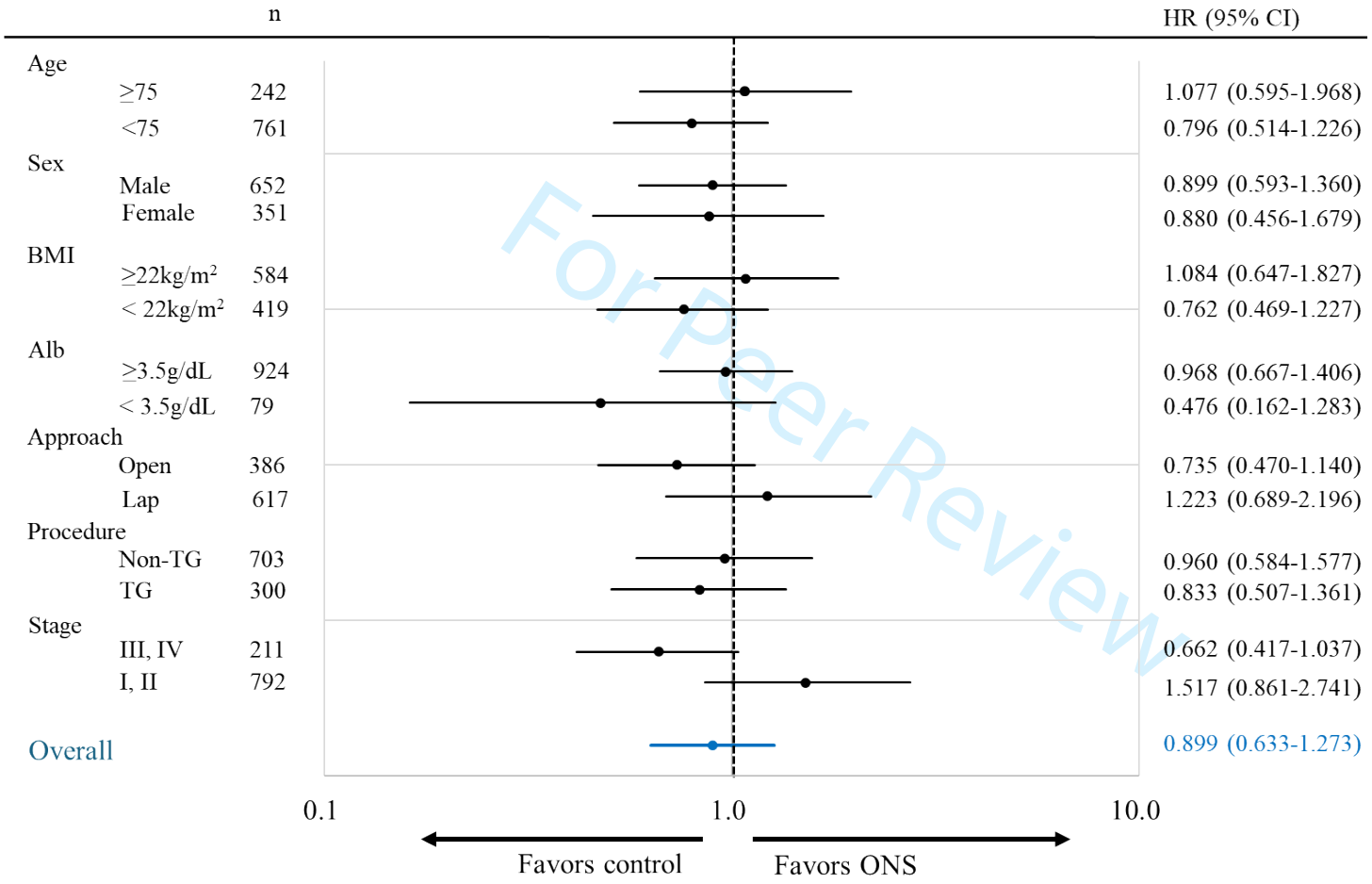
Figure 4



Number at risk							
Control group	503	481	452	424	399	382	323
ONS ≥200kcal/day group	221	216	206	194	179	170	135
ONS <200kcal/day group	182	178	169	158	146	142	123

Overall survival of the control group (n=503, blue solid line), ≥200 kcal/day ONS group (n=221, red solid line), and <200 kcal/day ONS group (n=182, red dotted line)

Figure 5



BMI, body mass index

Alb, albumin
Lap, laparoscopic
TG, total gastrectomy
ONS, oral nutritional supplements
HR, hazard ratio
95%CI, 95% confidence interval
Subgroup analysis was performed with a proportional hazards model for OS to evaluate statistical interactions between the treatment group and background.

Table 1. Background characteristics

	Control group	ONS group	P value
Sex (male/female)	330/173	322/178	0.689
Age, years	67.1±10.1	66.4±10.6	0.325
ECOG-PS (0/1/2)	443/54/6	446/50/4	0.757
Comorbidities (y/n)	321/181	323/177	0.829
Preoperative chemotherapy (y/n)	29/474	34/466	0.499
Preoperative BMI, kg/m^2	22.6±3.2	22.5±3.2	0.699
Type of gastrectomy			0.978
Total gastrectomy	152	148	
Distal gastrectomy	320	321	
Proximal gastrectomy	31	31	
Approach			0.956
Open	194	192	
Laparoscopic	309	308	
Operative time, minutes	280±78	281±75	0.914
Operative blood loss, ml	218±266	220±308	0.944
Pathological stage			0.999
IA	242	239	
IB	60	58	
IIA	62	57	
IIB	37	37	
IIIA	33	35	
IIIB	34	36	
IIIC	25	26	
IV	10	12	

Data are shown as the number of patients or the mean±standard deviation.

ECOG-PS, Eastern Cooperative Oncology Group-Performance Status
BMI, Body Mass Index
The pathological stage was classified according to the 14th edition of the Japanese Classification of Gastric Carcinoma[18].

Table 2. Postoperative adjuvant chemotherapy

	Control group	ONS group	P value
N	146	145	
Induction (y/n)	124 (84.9%) / 22	120 (82.8%) / 25	0.614
Regimen			0.485
S-1	107 (86.3%)	104 (86.7%)	
XELOX	5 (4.0%)	6 (5.0%)	
DS	6 (4.8%)	2 (1.7%)	
Others	6 (4.8%)	8 (6.7%)	
Continuation at 3 months (y (%) / n)	110 (75.3%) / 36	111 (76.6%) / 34	0.809
Continuation at 6 months (y (%) / n)	97 (66.4%) / 49	97 (66.9%) / 48	0.933
Continuation at 12 months (y (%) / n)	69 (47.3%) / 77	75 (51.7%) / 70	0.446

XELOX, capecitabine plus oxaliplatin
DS, 6 months of S-1 plus docetaxel, followed by 6 months of S-1

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Ref #16
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	17
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Ref #16
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	Ref #16
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Ref #16
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Ref #16
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Ref #16
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7-8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	-

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the trial ended or was stopped	11
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	13-14
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	14
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	14
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Ref #16
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	16-17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	17
Other information			
Registration	23	Registration number and name of trial registry	11
Protocol	24	Where the full trial protocol can be accessed, if available	Ref #16
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2, 17

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.