Randomized controlled trial to evaluate the safety and utility of early oral intake after gastric cancer resection-Influence of early oral intake on postoperative weight loss

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Randomized controlled trial to evaluate the safety and utility of early oral intake after gastric cancer resection—Influence of early oral intake on postoperative weight loss

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ABSTRACT

Backgroud

In recent years, enhanced recovery after surgery (ERAS) has been proposed in the field of gastrointestinal surgery. However, the safety and efficacy of early oral intake initiation after gastrectomy was not well established.

Patients and Methods

The present study is a subset analysis of patients in our hospital in a multicenter randomized controlled trial (UMIN000014042). Patients who underwent gastrectomy from January 2014 to December 2015 were divided into a group of 23 patients in the early oral intake group and a group of 22 patients in the conventional oral intake group according to the critical path, and length of stay, adverse events, and weight loss rate at three months postoperatively were examined.

Result

The postoperative length of stay tended to be shortened in the intervention group (intervention group 8.0 [8.0–10.0] days, control group 9.5 [8.0–10.3] days, P= 0.34). There was no significant difference with regard to date of possible hospital discharge and the factors used as indicators. Regarding weight loss rate at three months postoperatively, there was a tendency for the weight loss rate to be lower in the intervention group (8.3

[5.3-14.7%]) than in in the control group (15.2% [2.1-23.9%]) (P=0.123). There were no significant differences between the two groups with regard to incidence of adverse events of Clavien-Dindo classification grade II or higher (P＝1.00).

Conclusion

Subset analysis at our hospital revealed that early oral intake could be safely performed from 1POD. In addition, suggest that in comparison with the conventional path group, postoperative length of stay was shortened and weight loss rate was smaller. Future follow-up of patients and further study are necessary.

Keywords: After gastric cancer resection, postoperative length of stay, early oral intake, safety, weight loss

INTRODUCTION

In recent years, a comprehensive perioperative management method consisting of basic concepts including early oral intake through fast-track surgery or enhanced recovery after surgery (ERAS) has been proposed in the field of gastrointestinal surgery, including gastric cancer [1-5]. Such appropriate perioperative management measures are believed to promote postoperative recovery. However, unlike treatments such as operative treatment and chemotherapy, "proper perioperative management" is not standardized at present.

In Japan, gastric cancer is one of the most common cancers (1st among men, 3rd among women and 3rd among cases of colorectal cancer). Its prevalence is on a decreasing trend in the world, but in Japan, the morbidity rate is still increasing in both men and women as the population ages [6]. The basis of gastric cancer treatment is gastrectomy with lymph node dissection. Chemotherapy and best supportive care are performed when operative treatment is impossible, and the treatment methods have been standardized by the gastric cancer treatment guidelines of the Japanese Gastric Cancer Association [7].

Liu et al. report that early postoperative oral intake may be performed without increasing the risk of adverse events (risk ratio; RR: 0.97, 95% confidential intervals; 95% CI: 0.71 to 1.33, P <0.85) or readmission (RR: 1; 95% CI: 0.30 to 3.31, P = 1.00), and whether length of stay was significantly shortened as the meal start date was made earlier (weighted mead difference; WMD: -2.36, 95% CI: -3.37 to-1.34, P <0.0001) in a systematic review and meta-analysis [8]. In addition, Suehiro et al., Hirao et al., Yamada et al. compared the early intervention group in which a liquid diet was initiated on 2POD of gastric cancer with the control group receiving conventional nutrition management as a study at a single institution, and it was reported that postoperative hospital days were

significantly shortened in the early intervention group, and no difference in the incidence of postoperative complications between the early intervention group and the control group was noted [9-11].

Furthermore, Shimizu et al administered a questionnaire survey on meal start time, etc. to 354 facilities across Japan that perform 50 or more gastrectomies annually and obtained responses from 263 facilities. The survey results revealed that the median was 4 days for distal gastrectomy (DG) and total gastrectomy (TG) (both including laparoscopic surgery), and a correlation was found between meal start date and postoperative length of stay [12]. However, the median for the start of meals varied from 3 to 5 days, and the type of diet at the start varied from liquid diet to rice gruel in three degree, and each facility had its own postoperative diet, indicating the need for standardization of nutritional management methods after surgery for gastric cancer in Japan.

In Japan, the increase in medical expenses due to the super-aging society has been indicated as a problem, and reducing medical expenses has become an important issue. Thus, in order to reduce medical expenses due to hospitalization, shortening of the hospitalization period is also necessary from a social viewpoint. Therefore, in the present study, we standardized the meal start date and type of food after gastric cancer surgery, conducted a multi-center joint randomized controlled trial at 17 centers across Japan, and examined the safety of early oral intake, postoperative length of stay, and postoperative weight loss.

PATIENTS AND METHODS

Trial Group

The present clinical trial consisted of subset analysis at Kyushu University Hospital conducted at 17 centers nationwide. A data center independent of the study sites was established to perform test monitoring, data aggregation, and statistical analysis. A safety evaluation committee was established as a committee independent of the study site and reviewed the adverse events that occurred and made recommendations to the study site.

Patients

The selection criteria were as follows: patients aged 20 years to less than 80 years who were scheduled to undergo DG or TG (laparoscopy or laparotomy), clinical stage from IA to IIIB according to the cancer treatment protocol of the Japanese Gastric Cancer Association, and performance status of 0, 1 according to the Eastern Cooperative Oncology Group.

The primary exclusion criteria were as follows: patients in whom postoperative ventilatory management may be necessary, patients scheduled to undergo chemotherapy/chemoradiotherapy during hospitalization, patients who underwent preoperative chemotherapy or who were scheduled to undergo additional resection other than cholecystectomy, patients with multiple cancer, patients with a history of intestinal resection (small intestine polyps and appendectomy were permitted), patients at high-risk cases of severe cardiovascular complication, respiratory complication, liver damage, or renal damage, patients with allergy, and patients taking medication affecting intestinal hormones such as rikkunshito (liu jun zi tang; six gentlemen decoction). Cases in which

blood transfusion was performed intraoperatively and cases in which non-cholecystectomy was performed preoperatively were treated as inoperative cases.

The enrollment period for patients was from January 2014 to December 2015.

Enrollment/Assignment Methods

Enrollment and assignment of patients were performed centrally. The method of randomization featured the permuted block method (block size: 6) in which procedure (DG, TG) and facility were set as stratification factors.

In addition, as described later, patients assigned to the intervention group received meals rom the first day after the operation (postoperative day 1: 1POD), and in order to secure the time required for the order of the meals, enrollment/allocation was performed preoperatively rather than postoperatively.

Number of Patients (Sample Size)

The sample size settings for the entire population are shown. Assuming the postoperative length of stay obtained from the survey on nutritional management after gastric cancer surgery reported by Shimizu et al., when the sample size was calculated by setting the alpha error to 0.05 and the power to 0.9, it was calculated that at DG: 154 patients and TG: 206 patients, a significant difference between the groups was shown. Considering the dropout rate to be approximately 15%, the required number of patients was set to 170 for DG and 230 for TG in the multicenter randomized controlled trial.

Intervention Methods

Patients assigned to the intervention group were provided "iEAT®"from lunch on 1POD to dinner on 3POD. From 4POD, the meals provided at Kyushu University Hospital normally consist of starting with rice gruel in half degree, and after three meals it is changed to full rice gruel.

"iEAT®" is a food that has been adjusted with respect the physical properties of softness sot that it can be broken with the tongue, but has the appearance is the same as a normal meal as a result of the shape-retaining and softening process. Furthermore, regarding disintegrability and digestibility in artificial digestive juice, it has been shown to disintegrate more rapidly than ordinary foods and be digested to a slight residue [14].

The patients assigned to the control group were provided conventional path diet after surgery for gastric cancer in Kyushu University Hospital. In the case of DG, from 3POD, and in the case of TG, from 4POD, postoperative rice gruel in half degree is initiated, after three meals it is changed to full rice gruel. In addition, regarding infusion and snacking and other perioperative management methods, the conventional method of Kyushu University Hospital was used for both the intervention group and the control group, and no particular restrictions were put into place.

Evaluation (Outcomes)

The primary endpoint was the postoperative length of stay, and the secondary endpoint was the date of possible discharge. The day of possible discharge was set as the day when the indicators described below were all achieved. With reference made to the discharge criteria reported by Fearon et al. and Forie et al. [15, 16] and the 4th edition of gastric cancer treatment guidelines [7], the following seven items were used as indicators: no

need for infusion, fulfillment of the prescribed caloric intake (consumed food intake of 700 kcal or more), drain is removed, no epidural anesthesia is needed, no fever, and postoperative flatus/stool is confirmed.

Oral caloric intake amount was calculated by subtracting the amount of remaining food from the amount of provided food, calculating the eating rate, and multiplying the provided nutrient components by the eating rate.

In addition, the rate of decrease in preoperative body weight during hospitalization, vital signs, clinical laboratory data, changes in pain scale, presence or absence of onset of systemic inflammatory response syndrome (SIRS), incidence of adverse events, number/ratio of adverse events were assessed. Pain scale was evaluated within 30 minutes after each meal using a visual analog scale, and SIRS was evaluated using the SIRS diagnostic criteria of the American Thoracic Society (ATS).

Statistical Methods

In accordance with the study protocol, evaluation of efficacy was performed by per protocol set (PPS) and safety evaluation was performed by full analysis set (FAS). Quantitative data were expressed as median (minimum-maximum) and differences between the two groups were evaluated using Mann-Whitney U test or analysis of variance. The difference between the two groups of categorical data was evaluated using chi-square test or exact Wilcoxon-Mann-Whitney test. Oral calorie intake was evaluated as the median total calorie intake from 1POD to 5POD. Statistical analysis was performed using SPSS Version 24.0 (IBM Corp, Armonk, USA) with statistical significance set as $P < 0.05$.

RESULTS

The results of enrollment/assignment are shown in Fig. 1. Of the patients enrolled at our hospital, the intervention group: 23 patients (DG: 14 patients, TG: 9 patients), control group: 22 patients (DG: 16 patients, TG: 6 patients).

Regarding patient characteristics, there was no significant difference between the two groups for all items (Table. 1). The median oral intake start date in the intervention group was 1 day (23 patients) and in the control group, 3 days (17 patients) and 4 days (5 patients) (Table 1).

Regarding the primary endpoint of postoperative length of stay, the length was 8.0 (7.0-14.8) days in the intervention group and 9.5 (6.3-19.9) days in the control group, and there was no significant difference between the two groups (P=0.34) (Table 2).

There was no significant difference between the two groups regarding the date of possible discharge, which is the secondary endpoint (P=0.77). In addition, no significant difference was found between the two groups with regard to “duration to fulfill the prescribed caloric intake”, “drain placement duration”, and “duration until first postoperative flatus” as characteristics of day of possible discharge (P=0.53, P=0.07, P=0.20, respectively).

Regarding oral caloric intake, the caloric intake up to 5POD was as high as 3,088 (2,271–3,844) kcal in the intervention group and 2,658 (1,490–3,261) kcal in the control group, but no significant difference was noted (P＝0.059) (Fig. 2). In addition, upon observation of the relationship between oral caloric intake and pain scale during the early postoperative period (1 to 3 POD), a weak negative correlation between pain and caloric intake was noted (P<0.001, r=0.351) (Fig. 3).

There were no significant differences between the two groups with regard to the

incidence of adverse events of Clavien-Dindo classification Grade II or higher (P=1.00). The breakdown of the number of adverse events that occurred is also shown in Table 4.

As another safety indicator, the incidence of SIRS was significantly higher in 1 patient (4.3%) in the intervention group and in 6 patients (27.3%) in the control group (P=0.047). There was no significant difference between the two groups with regard to SIRS duration and rehospitalization within two weeks after surgery (P=0.27) (Table 5).

In addition, the weight loss rate preoperatively to 3 months postoperatively was analyzed in patients in which body weight was evaluated preoperatively and 3 months postoperatively (in both the intervention group and the control group, 14 patients in total). The intervention group (8.3 [5.4-14.7]%) and control group 15.2 (2.1-23.9)% small, but no significant difference was noted (Fig. 4).

Changes in clinical laboratory test values, vital signs, and pain scale showed similar changes between the two groups (data not shown).

DISCUSSION

Although various multicenter collaborative trials on treatment of gastric cancer have been conducted, many of the trials for dietary intake are reports of studies at a single institution. The present study is a subset analysis of a multicenter randomized controlled trial focusing on early oral intake.

In the present study, there was a significant difference between the intervention group and the control group with regard to the median oral intake start date (intervention group: 1POD (23 patients), control group: 3POD [17 patients] –4POD [5 patients], $P<0.001$), but in the control group, the results were similar to the median meal start date (4POD) at 262 facilities in the survey on nutritional management after gastric cancer reported by Shimizu et al.

By contrast, in the intervention group, oral intake of both DG and TG was possible from 1POD. After gastrectomy, early oral intake was considered to be clinically well tolerated when there was a good diet that was easy to digest in consideration of digestive symptoms and the amount of residual food was low. However, because super-elderly persons aged 80 years or older were not targeted, further examination is necessary.

The median postoperative length of stay for our subset was 8 days for the intervention group and 9.5 days for the control group in our subset. The results of this intervention group revealed that the postoperative length of stay of the intervention group was slightly shorter than that of all analysis subjects, and the safety of early oral postoperative intake after surgery appeared to be demonstrated. By performing nutrition intervention from 1POD, it appeared to be possible to increase oral caloric intake amount during hospitalization and shorten the number of days to achieve the prescribed oral caloric

intake amount, which is one of the indicators of day of possible discharge. Based on these findings, if the number of days to achieve the prescribed oral caloric intake could be shortened, discharge criteria may be able to be fulfilled at an early stage, resulting in shortening of the date of possible discharge and shortening of postoperative length of stay. However, because perioperative management has already been streamlined to some extent, there appear to be limitations to shortening of length by stay by intervention of early oral intake only. Intervention through nutritional guidance to eliminate post-operative dietary anxiety and intaking oral nutrition supplements (ONS) for nutrition that is lacking in preoperative diet, etc., are necessary along with nutritional management for postoperative wound healing in order to shorten postoperative length of stay.

Regarding oral calorie intake, total oral calorie intake (median value) up to 5POD was 3,088 kcal in the intervention group and 2,658 kcal in the control group. As a result of intervention, approximately 430 kcal could be added, there was no significant difference in nutritional indicators such as TP and Alb. Fujikuni et al. report that there was no significant difference in clinical laboratory values such as Alb, TTR, etc. during hospitalization between the group that underwent management in accordance with ERAS after gastrectomy and the control group, and the short duration of intervention period was considered as the cause for this [17]. In the present study also, the intervention period was three days, and the reason why no significant difference was noted in clinical laboratory data may be the short intervention period and the possibility that the amount of calories added was small.

Long-term problems after gastrectomy include weight loss. Hatao et al. examined the utility of postoperative ONS at 400 kcal/day for 12 weeks with DG and TG as targets [18]. It was reported that in the case of DG, no inhibition of postoperative weight loss by ONS

was noted as a result, in the case of TG, weight loss rate at 12 weeks after discharge was significantly smaller than that of the control group. These results also suggest that postoperative nutritional intervention has an effect of inhibiting weight loss.

Regarding the relationship between oral caloric intake and pain scale during the early postoperative period (1 to 3POD) pain scale, caloric intake was low in patients with severe pain. Feng et al. report that pain management is important in fast-track surgery and that appropriate pain management promotes early ambulation and oral intake after surgery [4]. These results also suggest that pain management is important, but because there were patients with low caloric intake even when the pain scale was low, in addition to pain management, it is also possible that oral caloric intake during the early postoperative period may be affected by the presence or absence of appropriate nutritional guidance to eliminate the anxiety of the patient's diet. In order to promote early oral intake, it is necessary to construct a system of multi-professional collaboration centered around patients and to remove the anxiety concerning living including postoperative meals by providing preoperative nutritional guidance and living guidance. Regarding safety assessment, adverse event rates for RCTs cited in systematic reviews and meta-analyses on ERAS® after gastrectomy to date have been reported as 18.1-23.6% in the ERAS group and 22.8-24.3% in the control group [4,8]. The adverse event rate in the present study was 4.3% in the intervention group and 4.5% in the control group, which was lower than previously reported. With regard to dehiscence, which is especially considered to be a risk among adverse events related to early oral intake, Willucutts et al. report that the incidence was similar between an early oral intake and conventional group after gastric cancer surgery (early oral intake group: 3.4%, conventional group: 3.9%) [19]. In the present study, dehiscence was not noted in either group, and it appears that early oral

intake after gastric cancer surgery is not a risk factor for dehiscence. In the present study, there was no significant difference in adverse event rates between the intervention group and the control group, and there was no causal relationship with food intake. However, in the entire population, many adverse events occurred in the early intervention group [20], and it is also possible that the facility gap had an influence.

Under the selection criteria of the present study, the target patient age was from 20 to 80 years, so the utility of early oral intake after gastric cancer resection in super-elderly persons is unclear. Furthermore, in the present study, intervention was performed using I-Eat®, which has excellent appearance and physical properties as a starting food, but it is unclear if similar results can be obtained when using other food types, such as using liquid food or semi-solid food such as jelly as the starting food. In recent years in Japan, the Essential Strategy for Early Normalization after Surgery with Patient's Excellent Satisfaction (ESSENSE) project in which the Japanese Society for Surgical Metabolism and Nutrition is mainly engaged as the Japanese version of ERAS® is in progress [21]. One of the goals is to shorten the length of stay, but under ESSENSE, the highest importance is placed on patient satisfaction, and the key is how to implement perioperative management from the perspective of the patient. Including the present study, research on perioperative management will not only leads to shortening of length of stay, but also improvement of patient satisfaction such as inhibition of postoperative weight loss, and it is the authors' opinion that the evidence can be used in clinical practice and reflected in medical economic effects.

CONCLUSION

The present analysis is a subset analysis of Kyushu University Hospital in a multicenter joint randomized controlled trial conducted across Japan. The results of this study confirmed the safety of early oral intake and suggest the utility of early intervention from the viewpoint of shortening postoperative length of stay and nutritional management.

ACKNOWLEDGMENTS

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Disclosure

The present study is a partial trial of a multicenter randomized controlled trial conducted in accordance with the Ethical Guidelines for Clinical Trials (Ministry of Health, Labour and Welfare notification) in compliance with the ethical principles based on the Declaration of Helsinki under the approval of the institutional review board of Kyushu University Hospital (Reception No: 25067 Kyushu University Graduate School No. 961). Informed consent was obtained in writing from all enrolled patients. Moreover, in the present study, patients were enrolled in the Clinical Trials Registry of the University

hospital Medical Information Network (UMIN) (UMIN000014042). The present study was conducted based on entrustment agreement with EN Otsuka Pharmaceutical Co., Ltd., and the company provided research funds and "iEAT®", and we received support from the company in preparing the present manuscript.

The author and co-authors declare no individual conflicts of interest with EN Otsuka Pharmaceutical Co., Ltd.

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Figure legends

Figure 1

Patient disposition

Figure 2

Total caloric intake up to 5POD. Mann-Whitney U test was used to perform analysis.

Figure 3

Relationship between oral caloric intake and pain scale

Figure 4

Weight loss rate at 3 months postoperatively. Mann-Whitney U test was used to perform analysis.

Tables

Table.1 Patient Characteristics

	Intervention group (n=23)	Control group (n=22)	P
Procedure	DG: 14　TG: 9	DG: 16　TG: 6	0.53
Approach	Laparoscopy: 23 Laparotomy: 0	Laparoscopy: 21 Laparotomy: 1	0.50
Reconstruction method	B-1: 14　R-Y: 9	B-1:12　R-Y:10	0.77
Weight	56.2（48.3-67.5）	56.1（50.4-65.9）	0.82
Height	163.9（153.0-167.0）	166.1（158.0-170.3）	0.13
Age	65.0（60.0-73.0）	63.5（58.0-72.3）	0.46
Sex	Men: 13　Women: 10	Men: 17　Women: 5	0.21
Past medical history	Yes: 8　No: 15	Yes: 7　No: 15	1.00
Complication	Yes: 1　No: 22	Yes: 1　No: 21	1.00
PS	0：23　1：0	0：22　1：0	—
Operative duration	290.0（256.0-349.0）	295.5（237.5-339.3）	0.77
Hemorrhage volume	54.0（15.0-75.0）	45.5（33.8-103.3）	0.26
cStage	IA: 12　IB: 4　IIA: 0 IIB: 3 IIIA: 3 IIIB: 1	IA: 16　IB: 1　IIA: 4 IIB] 0　IIIA: 1	0.50
pStage	IA: 10　IB: 4　IIA: 2 IIB: 3 IIIA: 2　IIIB: 2 IIIC: 2	IA: 11 IB:1　IIA: 1 IIB:1 IIIA] 5　IIIC: 2 IV:1	0.49

Analysis of variance was performed for numerical data. Chi-square test was performed for categorical data.

Table 2 Pre- and postoperative length of stay

	intervention group (n=23)	Control group (n=22)	P
Postoperative length of stay	8.0（8.0-10.0）	9.5（8-10.3）	0.34

Mann-Whitney U test was used to perform analysis.

Table 3 Day on which discharge is possible

	intervention group (n=23)	Control group (n=22)	P
Period to meet the prescribed meal amount	4.0（3.0-5.0）	4.0（3.0-5.0）	0.53
Infusion implementation period	3.0（2.0-4.0）	4.0（3.0-4.0）	0.23
Drain placement duration	4.0（3.0-4.8）	4.0（4.0-4.3）	0.07
Duration of epidural anesthesia	2.0（2.0-5.0）	2.0（0-4.0）	0.10
Period until body temperature falls below 37°C	2.0（1.0-3.0）	2.0（1.0-3.0）	0.82
Day of first postoperative flatus	2.0（2.0-3.0）	3.0（2.0-3.0）	0.20
Day of first postoperative defecation	4.0（3.0-5.0）	4.0（3.0-5.0）	0.65
Day on which discharge is possible	5.0（4.0-5.8）	5.0（4.0-6.0）	0.77

Mann-Whitney U test was used to perform all analyses.

Table 4 Grade 2 or higher adverse events under Clavien-Dindo classification

	Intervention group (n=23)	Control group (n=22)
Delayed gastric emptying	1 (Grade3)	0
Pancreatic fistula	0	0
Dehiscence	0	0
Intra-abdominal abscess	0	0
Ileus	0	0
Postoperative hemorrhage	0	0
Pneumonia	0	0
Tachycardia	0	1 (Grade2)

Table 5 Other safety indicators

	intervention group (n=23)	Control group (n=22)	P
Rehospitalization within 2 weeks after discharge	Yes: 2 No: 21	Yes: 0 No: 22	0.489
Presence of SIRS	Yes: 1 No: 22	Yes: 6 No: 16	0.047
Duration of SIRS	1（0-2）	1（1-2）	0.27

*Analysis of variance was performed for numerical data. Chi-square test was performed for categorical data.

The presence or absence of SIRS was determined from clinical laboratory data and vital signs using the SIRS diagnostic criteria of the American Thoracic Disease Society (American Thoracic Disease Society, 1991).

Figures

Fig. 1

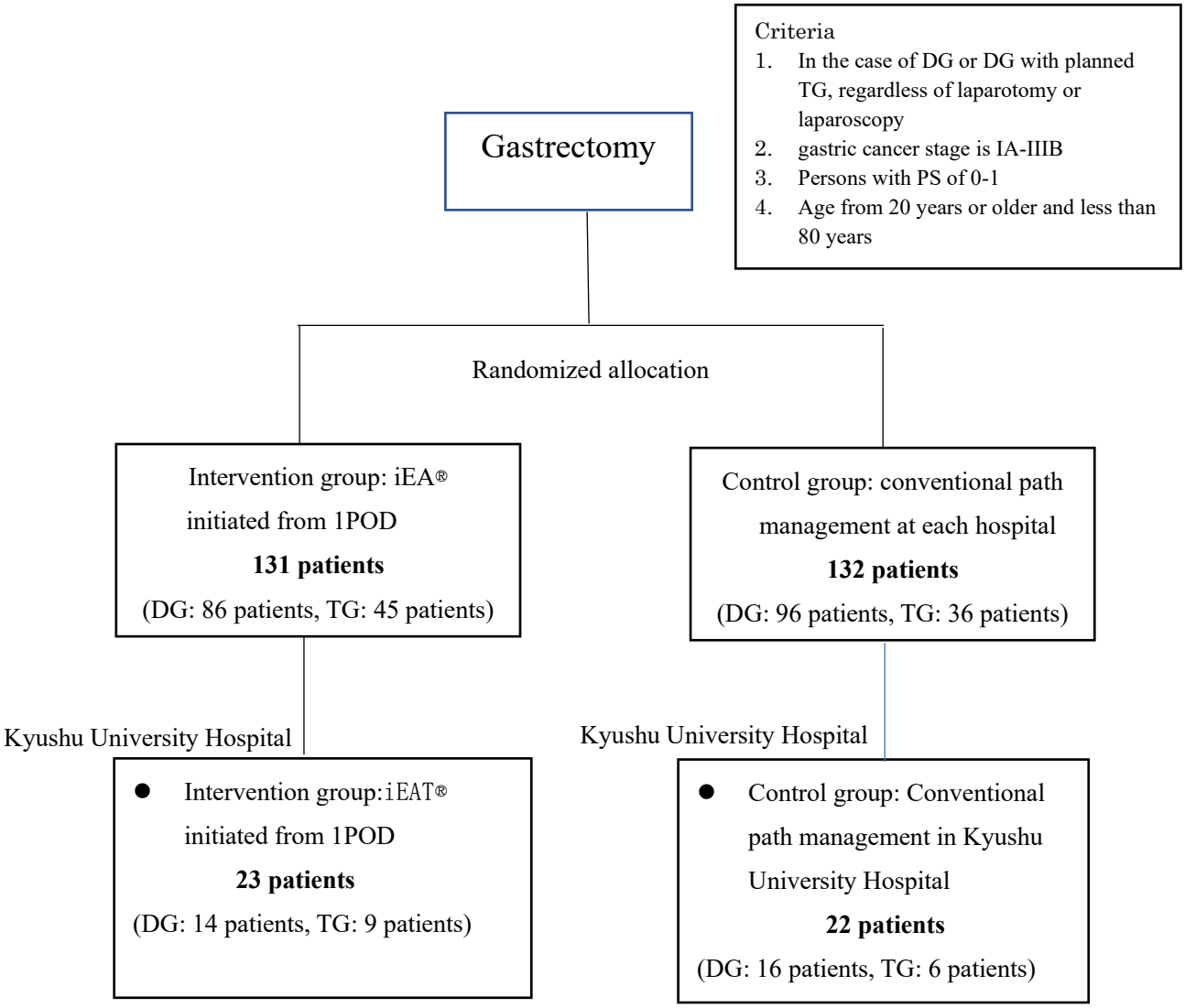
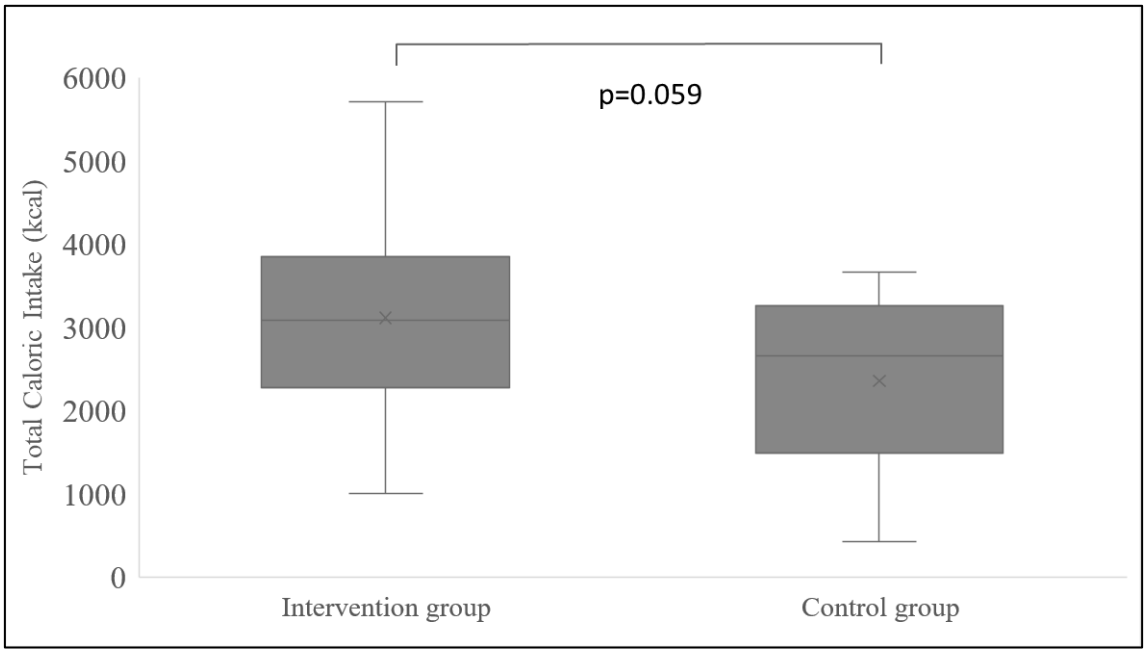


Fig. 2


p=0.059
Total Caloric Intake (kcal)
6000
5000
4000
3000
2000
1000
0
Intervention group
Control group

.

Fig. 3

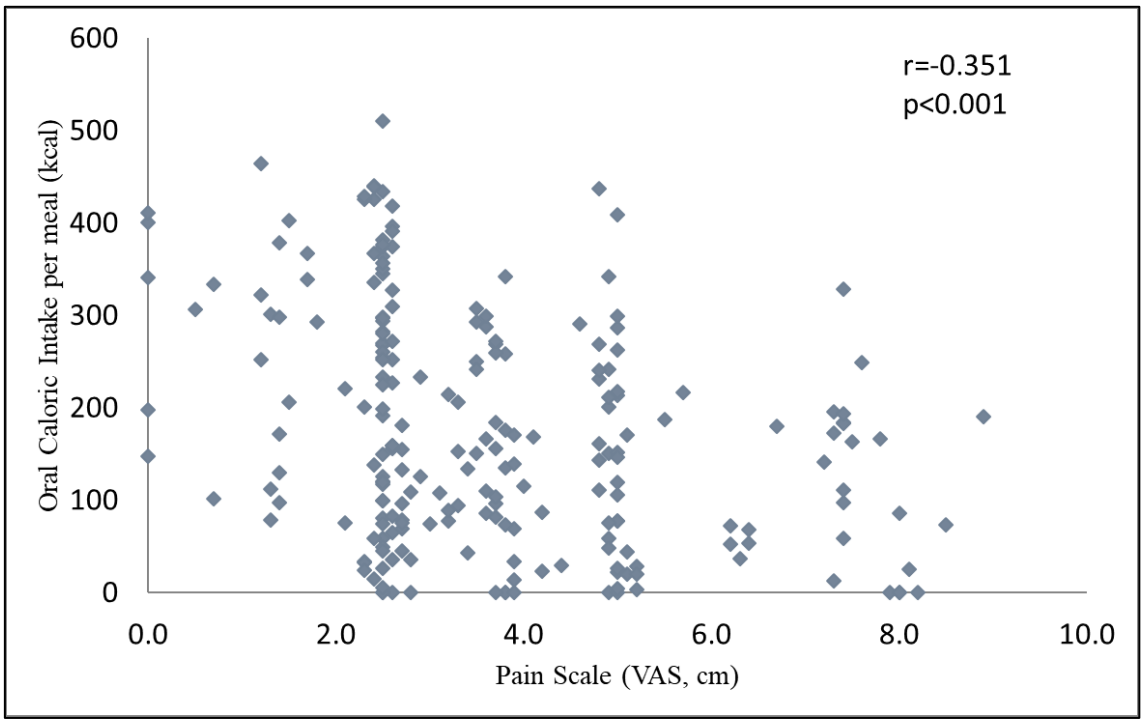
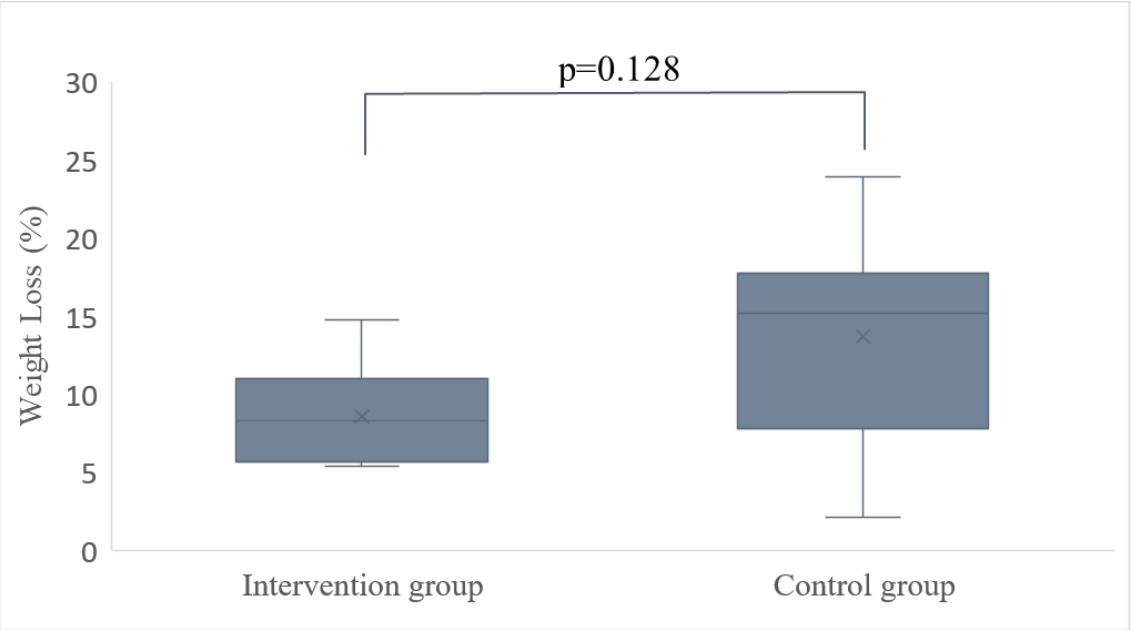

r=-0.351
p<0.001
Oral Caloric Intake per meal (kcal)
600
500
400
300
200
100
0
0.0
2.0
4.0
6.0
8.0
10.0
Pain Scale (VAS, cm)

Fig. 4



Mann-Whitney U test was used to perform analysis.