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ORIGINAL ARTICLE

A comparison of postoperative quality of life and dysfunction after Billroth I and Roux-en-Y reconstruction following distal gastrectomy for gastric cancer: results from a multi-institutional RCT

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Abstract
Background Both Billroth I (B-I) and Roux-en-Y (R-Y) reconstructions are commonly performed as standard procedures, but it has yet to be determined which reconstruction is better for patients. A randomized prospective phase II trial with body weight loss at 1 year after surgery as a primary endpoint was performed to address this issue. The current report delivers data on the quality of life and degree of postoperative dysfunction, which were the secondary endpoints of this study.

Methods Gastric cancer patients who underwent distal gastrectomy were intraoperatively randomized to B-I or R-Y. Postsurgical QOL was evaluated using the EORTC QLQ-C30 and DAUGS 20.

Results Between August 2005 and December 2008, 332 patients were enrolled in a randomized trial comparing B-I versus R-Y. A mail survey questionnaire sent to 327 patients was completed by 268 (86.2%) of them. EORTC QLQ-C30 scores were as follows: global health status was similar in each group (B-I 73.5 ± 18.8, R-Y 73.2 ± 20.2, $p = 0.87$). Scores of five functional scales were also similar. Only the dyspnea symptom scale showed superior results for R-Y than for B-I (B-I 13.6 ± 17.9, R-Y 8.6 ± 16.3, $p = 0.02$). With respect to DAUGS 20, the total score did not differ significantly between the R-Y and B-I groups (24.8 vs. 23.6, $p = 0.41$). Only reflux symptoms were significantly worse for B-I than for R-Y (0.7 ± 0.6 vs. 0.5 ± 0.6, $p = 0.01$).

Conclusions The B-I and R-Y techniques were generally equivalent in terms of postoperative QOL and dysfunction. Both procedures seem acceptable as standard reconstructions after distal gastrectomy with regard to postoperative QOL and dysfunction.

Keywords Distal gastrectomy · Roux-en-Y · Billroth I · QOL · Randomized trial

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Introduction

Both Billroth I (B-I) and Roux-en-Y (R-Y) anastomoses have been performed as standard procedures after distal gastrectomy [1]. B-I was once commonly performed because this procedure was simple and the foods passed physiologically [2]. R-Y reconstruction was chosen to

prevent postoperative alkaline reflux gastritis and esophagitis of the remnant stomach after distal gastrectomy [3–5]. In addition to these problems, some surgeons reported postoperative carcinogenesis of the remnant stomach [6–8]. In contrast, R-Y stasis syndrome, which occurs occasionally during the early postoperative period, is one of the major complications of R-Y reconstruction [9–11]. Most surgeons choose a reconstruction procedure according to personal preferences or degree of experience. It is difficult to select the reconstruction procedure scientifically because few studies have directly compared the B-I and R-Y techniques.

We performed a randomized prospective multicenter trial comparing B-I and R-Y reconstruction. The primary endpoint was a comparison of body weight loss 1 year after surgery. Postoperative quality of life (QOL) was one of the secondary endpoints of the study.

QOL evaluation using questionnaire surveys was once considered to be unreliable because of their subjective nature. However, questionnaires have since been developed and validated as important tools for comprehensively assessing physical conditions. They are now considered to be reliable measurements for evaluating surgical outcomes, especially in randomized clinical trials.

This study is the first to use a questionnaire survey to evaluate QOL and dysfunction following B-I and R-Y reconstructions after distal gastrectomy.

Methods

Study design

This prospective trial was initiated in August 2005. We conducted a multicenter randomized phase II study that was approved by the institutional review boards of all participating hospitals and was conducted in accordance with the Declaration of Helsinki. Our hypothesis was that R-Y reconstruction would result in lower postoperative body weight loss than the B-I technique while maintaining similar surgical results. The primary endpoint was postoperative body weight loss, and secondary endpoints were surgical morbidity and postoperative QOL.

Patients

After completion of the informed consent process, patients were included in the study if they met the following eligibility criteria: histologically proven gastric cancer, a lack of non-curative surgical factors except for positive lavage cytology, age between 20 and 90 years, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, no prior chemotherapy or radiation therapy, and no history of gastrectomy or other malignancy (except carcinoma in situ of uterus cervical cancer and focal cancer in adenoma of colorectal cancer) during the past 5 years. All patients gave written informed consent before undergoing randomization. Exclusion criteria included: history of laparotomy (except appendectomy and laparoscopic cholecystectomy), interstitial pneumonia or pulmonary fibrosis, severe heart disease, liver cirrhosis or active hepatitis, chronic renal failure, severe diabetes (HbA1c $\geq$9.0%), and severe reflux esophagitis. After the surgeon confirmed the above eligibility and exclusion criteria immediately following the initial laparotomy, patients were intraoperatively randomized to either the B-I group or the R-Y group. Randomization was performed by the minimization method according to BMI and institutional preferences.

In our surgical study group, the Osaka University Clinical Research Group for Gastroenterological Study, the standard reconstructive method following distal gastrectomy has been the BI reconstruction because of the physiological advantage of allowing food to pass through the duodenum and the surgical simplicity of the BI reconstructive method in comparison with the RY method. It has been reported that the rate of body weight loss at 1 postoperative year was 10–15% following BI operations [12]. In this study we hypothesized that relative to the BI operation, the RY operation may decrease body weight loss at 1 year after surgery by 5%.

The sample size was determined to provide 80% power to detect an effect size of 5% using a one-sided alpha error of 5% under the normal distribution with a standard deviation of 0.1 in both groups. The primary endpoint was evaluated by t test. The planned sample size was 320 patients (160 for each arm), allowing for a 10% dropout rate at the postoperative 1-year point.

Surgical treatment

In both groups, the surgeon performed standard treatment for gastric cancer according to the Japan classification of gastric carcinoma [13]. As a result of this study's design as a multicenter trial, a variety of procedures were employed during reconstructions, including use of mechanical suture devices or hand-sewn techniques, choice of antecolic or retrocolic routes during the R-Y approach, and laparoscopic or open procedures. There were no detailed regulations concerning each reconstruction procedure so as to provide patients with the highest quality of care based on the specific institution in which they were hospitalized. The only requirement was an R-Y limb length of 30 cm, because this length could affect postoperative nutrition and R-Y stasis.

Patients were enrolled from 18 hospitals belonging to the Osaka University Clinical Research Group for Gastroenterological Surgery. All operations were performed or

supervised by senior surgeons who were members of the Japaneses Gastric Cancer Association. Patients were followed up every 3 or 6 months until 5 postoperative years. Adjuvant therapy was not specified in the protocol.

Assessment of QOL

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) (Japanese version) is a 30-item cancer-specific integrated system for assessing the health-related QOL of cancer patients [14–16]. The questionnaire comprises five scales related to function (physical role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health and QOL scale, and single items for the assessment of additional symptoms commonly reported by cancer patients (e.g., dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea), and perceived financial impact of the disease and treatment. All items are scored using 4-point Likert scales. All scales were linearly transformed to a 0 to 100 score, with 100 representing the best global health status or functional status or the worst symptom status.

Assessment of postoperative dysfunction

The Dysfunction After Upper Gastrointestinal Surgery for Cancer (DAUGS 20) scoring system was to assess postoperative dysfunction. The DAUGS 20 has previously undergone extensive development and testing [17, 18], and was originally developed for simultaneous use with the EORTC QLQ-C30. The patients rated 20 items related to postoperative gastrointestinal dysfunction according to a scale of 1 (not at all) to 5 (very severe). High scores indicated more severe dysfunction. The 20 items were divided into the following 7 categories: (1) diarrhea or soft feces, (2) pain, (3) dumping-like symptoms, (4) food passage dysfunction, (5) nausea and vomiting, (6) decreased physical activity, and (7) reflux symptoms.

Questionnaire survey

A self-administered questionnaire that included the EORTC QLQ-C30 and DAUGS 20 was dispatched by mail 3 months after the last case had been registered. The patients completed the questionnaire and returned it by mail to the clinical study register center. Because this questionnaire survey was not administered by a primary care doctor, bias was minimized.

Statistical analysis

Stastical analysis was performed with the JMP stastical package, version 8 (SAS, Cary, NC, USA). Data are expressed as means ± SD. Total scores for the EORTC QLQ-C30 and DAUGS 20 were compared between the two groups using the Mann–Whitney test. p values of less than 0.05 were considered significant.

Results

Questionnaire, compliance, and missing data

A CONSORT flowchart of the trial design is shown in Fig. 1. A total of 332 adult patients (220 men and 112 women) with gastric cancer were enrolled: 163 in the B-I group and 169 in the R-Y group. Five cases were excluded because of errors in which the reconstruction procedure was performed ($n = 3$) or death ($n = 2$). Of the 327 participants, 282 (86.2%) returned the questionnaire sheets. Fourteen cases were excluded from the analysis because of curability C (definite residual tumor) and recurrence ($n = 9$) and ongoing adjuvant chemotherapy ($n = 5$), which would strongly affect postoperative QOL and dysfuntion. Finally, 268 cases (132 B-I, 136 R-Y) were analyzed for the evaluation of postoperative QOL. The median observation period was 21 months (range 3–34). The clinicopathological characteristics of the 268 patients are summarized in Table 1. No significant differences were observed in age, sex, depth of tumor invasion, or stage of gastric cancer. The rates of distant and lymphatic metastasis were also similar. The laparoscopic approach was selected in 29 of 163 patients who underwent B-I reconstruction and 33 of 169 patients who were treated by R-Y. Blood loss did not differ between the two groups. The operative time in the R-Y group was significantly longer than in the B-I group (214 vs. 180 min, respectively, $p < 0.0001$).

EORTC QLQ-C30

The results of global health status and functional scales of EORTC QLQ-C30 are shown in Fig. 2. The mean scores for global health status were very similar in both groups (B-I 73.5 ± 21.3, R-Y 73.2 ± 20.2, $p = 0.87$). As for the functional scales, B-I was not significantly superior to R-Y on only the cognitive scale (B-I 80.3 ± 18.1, R-Y 75.7 ± 21.3, $p = 0.06$). There were no significant differences between the two groups on the other four functional scales (physical, role, emotional, and social functioning). The results of symptom scales of EORTC QLQ-C30 are shown in Fig. 3. Regarding symptom scales, B-I was significantly inferior to R-Y on the dyspnea scale (B-I 13.6 ± 17.9, R-Y 8.6 ± 16.3, $p = 0.02$). There were no significant differences on the other eight symptom scales (fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation, diarrhea, financial difficulties).

Fig. 1 Consort flow chart

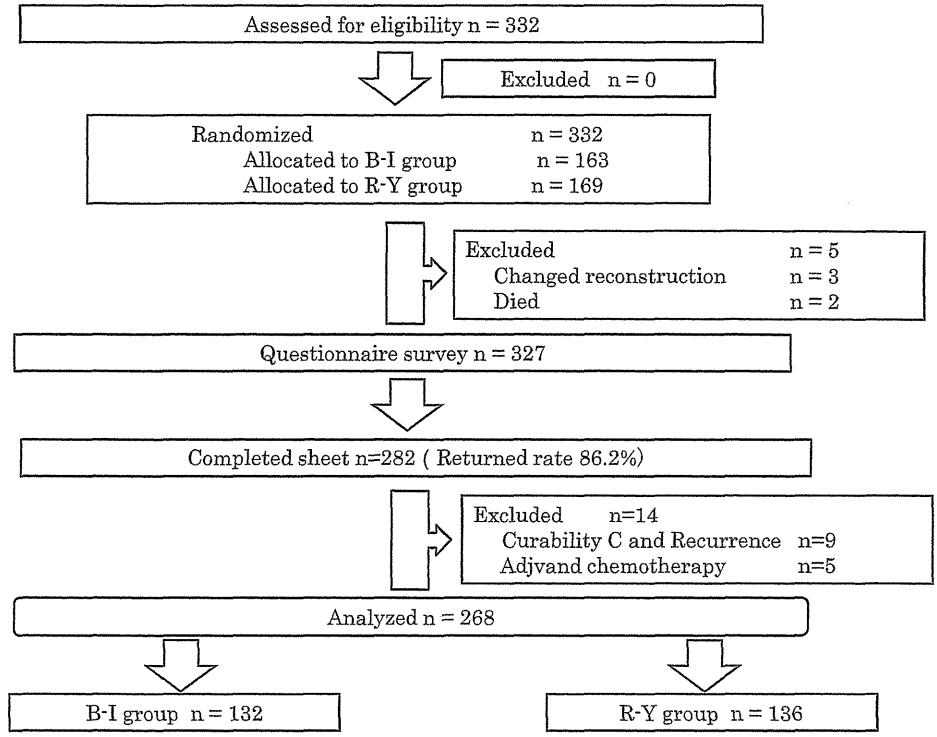


Table 1 Characteristics and operative results of patients who underwent distal gastrectomy and answered the questionnaire survey

	B-I group (n = 132)	R-Y group (n = 136)	p
Sex (male/female)	105/58	113/53	0.48*
Age	64.5 ± 9.8	64.1 ± 10.5	0.68†
Height (cm)	161.3 ± 8.3	161.1 ± 9.7	0.89†
Weight (kg)	58.3 ± 9.7	59.5 ± 11.3	0.29†
Macroscopic appearance (0/1/2/3/5)	98/5/17/9/3	100/8/13/14/1	0.50**
Location (L/M)	92/40	91/45	0.62*
Tumor size (cm)	2.9 ± 1.7	2.9 ± 1.5	0.93*
Approach (open/laparoscopic)	134/29	136/33	0.68*
Dissection level (D1+/D2/D3)	58/105/0	59/106/1	0.61*
Operation time (min)	180 ± 48	214 ± 44	<0.0001†
Blood loss (ml)	210 ± 230	203 ± 153	0.78†
m/sm/mp/ss/se	48/54/15/11/4	45/57/17/13/4	0.98**
pN (−/+)	107/25	104/32	0.35*
pStage (IA/IB/II/IIIA/IIIB/IV)	91/24/15/2/0/0	90/24/14/6/1/1	0.43**

Clinical findings and staging classifications are described according to the Japanese Classification of Gastric Carcinoma

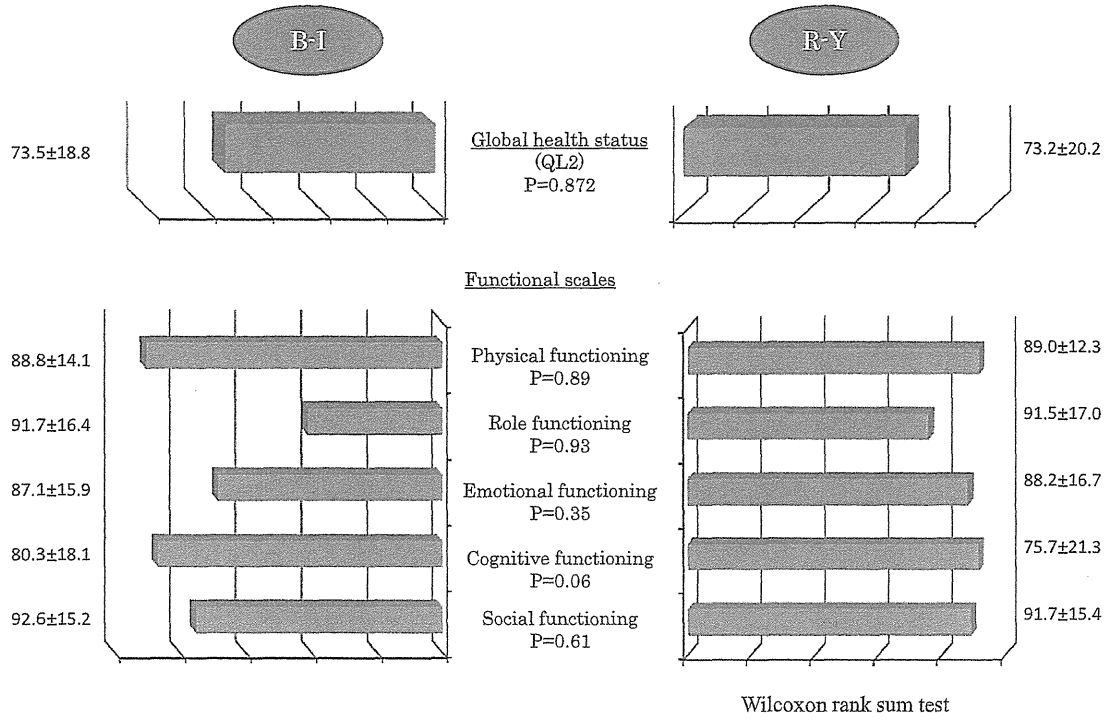
* χ^2 test

** Mann-Whitney U test

† Wilcoxon rank sum test

DAUGS 20 scoring system

The results of the DAUGS 20 score are shown in Fig. 4. The total score of the DAUGS 20 was very similar in both groups (B-I 24.8 ± 11.6, R-Y 23.6 ± 11.4, $p = 0.41$). Subclass analysis showed that B-I was significantly worse in terms of reflux symptoms (B-I 0.7 ± 0.6, R-Y 0.5 ± 0.6, $p = 0.01$). There were no significant differences between the two groups in terms of the other six subclasses: diarrhea or soft feces (B-I 2.1 ± 1.3, R-Y 2.0 ± 1.2, $p = 0.7$), pain (B-I 1.1 ± 0.9, R-Y 1.2 ± 0.9, $p = 0.64$), dumping-like syndrome (B-I 1.8 ± 1.0, R-Y 1.8 ± 1.0,



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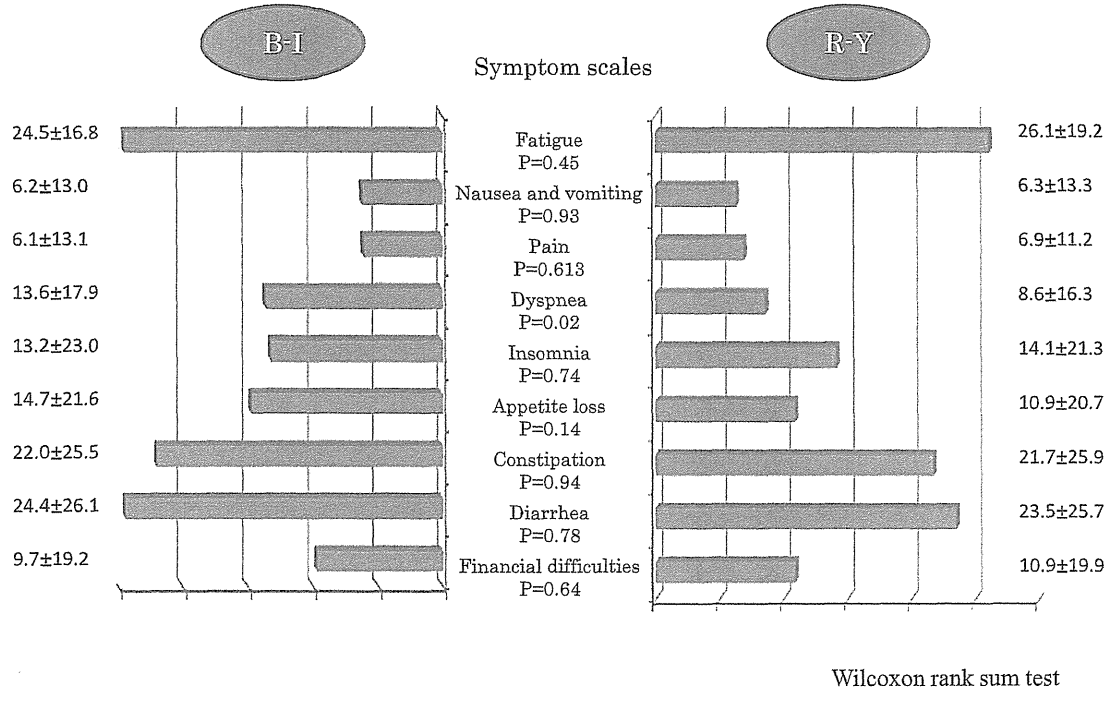
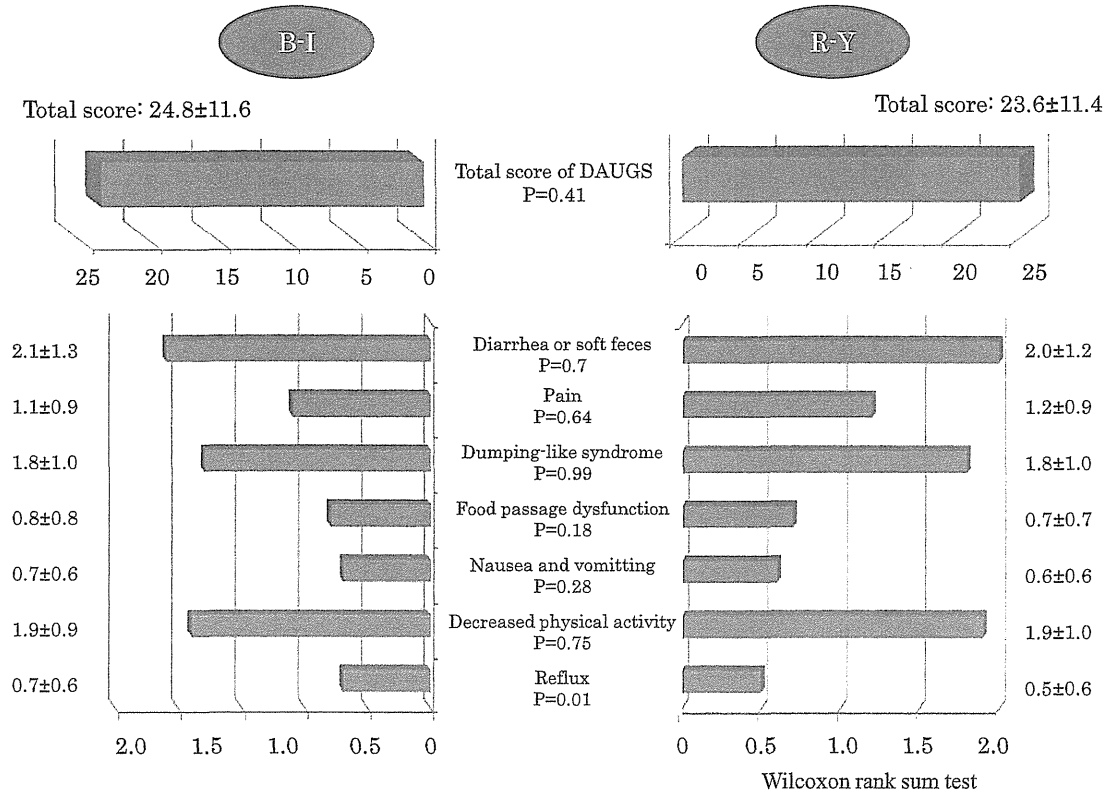


Fig. 3 B-I was significantly inferior to R-Y on the dyspnea scale (B-I 13.6 ± 17.9, R-Y 8.6 ± 16.3, $p = 0.02$). There were no significant differences on the other eight symptom scales (fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation, diarrhea, financial difficulties)



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$p = 0.99$), food passage dysfunction (B-I 0.8 ± 0.8, R-Y 0.7 ± 0.7, $p = 0.18$), nausea and vomiting (B-I 0.7 ± 0.6, R-Y 0.6 ± 0.6, P = 0.28), and decreased physical activity (B-I 1.9 ± 0.9, R-Y 1.9 ± 1.0, $p = 0.75$).

Comparison of survey scores every 6 months

The global health status scores and total DAUGS 20 scores were summarized every 6 months (Fig. 5). There were significant differences in total DAUGS 20 scores during the first 6 months (B-I 22.8 ± 13.7, R-Y 32.4 ± 8.9, $p = 0.04$). There was no significant difference in global health status and total DAUGS 20 scores at other periods between the B-I group and the R-Y group.

Discussion

This prospective randomized trial showed no significant differences between the B-I and R-Y groups in terms of postoperative QOL and dysfunction, as evaluated by a questionnaire using the EORTC QLQ-C30 and DAUGS 20 scales. In this study, body weight loss at 1 year after surgery, which was the primary endpoint in this study, was 9.1% for the B-I group and 9.7% for the R-Y group ($p = 0.39$). Body weight change would be related to the QOL and dysfunction. The results of the questionnaire survey did not contradict the results of body weight loss. This study included a larger number of cases than other randomized clinical trials evaluating postoperative QOL and dysfunction after distal gastrectomy. It was particularly interesting that patients in the two groups evaluated their QOL and dysfunction almost equally despite the significant anatomic differences between the reconstruction procedures.

Prognosis or overall survival has been the most important factor when evaluating cancer treatments. Since cancer is now detected more frequently in its early stages and postoperative prognosis has improved, postoperative QOL and dysfunction have come to be acknowledged as important endpoints in addition to oncologic outcomes and safety issues. For example, Kim et al. [19] reported that laparoscopy-assisted distal gastrectomy was superior to conventional open distal gastrectomy in terms of QOL outcomes 3 months after surgery. Precise evaluation of the effectiveness of minimally invasive surgery is difficult; however, if the oncologic outcome is equal between procedures, QOL findings will be useful in deciding on the

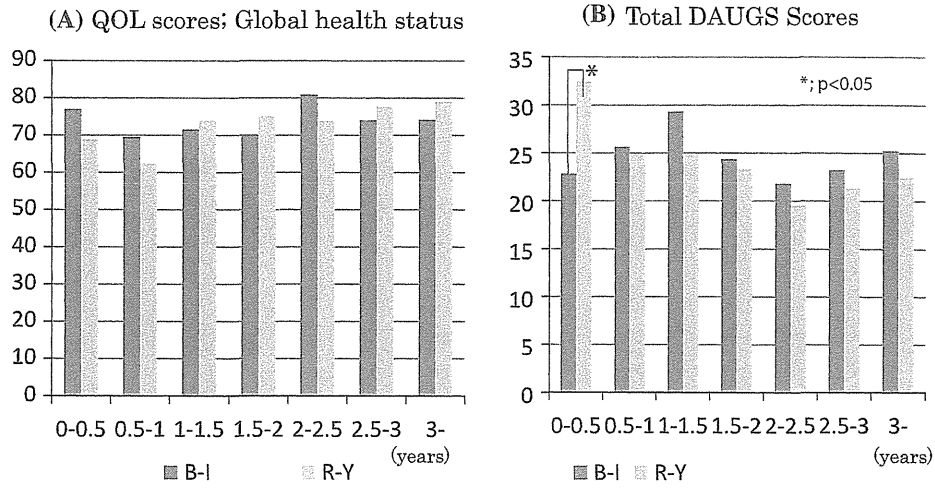

Fig. 5 There were significant differences in total DAUGS 20 scores during the first 6 months (B-I 22.8 ± 13.7, R-Y 32.4 ± 8.9, $p = 0.04$). There was no significant difference in global health status and total DAUGS 20 scores at other periods between the B-I group and the R-Y group

optimal operative approach. The Japanese version of the EORTC QLQ-C30 has been developed and validated. Kobayashi et al. [20] used this version to prospectively compare postoperative health-related QOL among gastrectomy patients and found clear difference among the operative procedures.

The DAUGS 20 scale was designed to objectively assess gastrointestinal dysfunction after surgery for upper gastrointestinal cancer. The scale has already been validated in the field of upper intestinal cancer [17, 18]. We found no significant difference between R-Y and B-I procedures in terms of overall postoperative dysfunction. However, there were significant differences in total DAUGS 20 scores during the first 6 months (B-I 22.8 ± 13.7, R-Y 32.4 ± 8.9, $p = 0.04$). Especially each score of food passage dysfunction and nausea and vomiting tended to be worse in the R-Y group (not significant). This may be weakened to gastrointestinal motility and delayed gastric emptying with R-Y. In this series, the frequency of nausea, vomiting, and discontinuation of food intake were significantly lower in the B-I group than in the R-Y group (3.7 vs. 12.4%, $p = 0.0027$; 3.1 vs. 8.9%, $p = 0.022$; 4.3 vs. 12.4%, $p = 0.0064$, respectively). Frequency of delayed gastric emptying in the B-I group was lower than in the R-Y group (4.3 vs. 9.5%, $p = 0.057$). In general, Roux en Y stasis occurred within the postoperative 1st month. Minor symptoms could not be detected during the hospital stay, and small amounts of nausea or vomiting might have occurred at home. Our questionnaire survey might detect this small difference between B-I and R-Y related gastrointestinal motility during the first 6 months.

The EORTC QLQ-C30 showed significant differences only in dyspnea. This symptom seemed to be physiologically unrelated to postoperative complications. Patients who received B-I gastrectomy sometimes complained of heartburn. This score seemed to be affected by esophagitis caused by bile and gastric juice reflux. In the analysis of partial items of the DAUGS, reflux symptoms also obviously appeared in the B-I group. If this limitation can be overcome, we can feel confident in continuing to perform B-I reconstructions. While Shibata reported that semifundoplication following B-I reconstruction prevented this difficulty, further surgical intervention following gastrectomy is less than ideal [21].

The questionnaire survey in the current study was performed only once for each patient and at varying time points after surgery, since co-investigators in this multi-institutional study did not agree to perform the survey several times and at regular intervals. Such a design would have delivered more convincing data, but would have been too much of a burden for the co-investigators. An alternative design would have been to perform all the surveillances at a fixed time point, such as at 1 year postoperatively. However, it was not possible to decide on the optimal time point for performing the surveillance at the time this study was designed. It has now become clear how the scores vary at different time points, and further study to confirm the differences between B-I and R-Y can now be designed and proposed.

In general, from the point of view of the surgeon, B-I reconstruction is considered to be simple and relatively easy. For the patient, nutritional and hormonal advantages might exist in this physiological route. It is easier to treat common bile duct stones using a gastrointestinal fiberscope after B-I reconstruction. In contrast, the advantage of R-Y reconstruction is thought to be less anastomotic leakage and infrequent reflux esophagitis and gastritis. However, disadvantages include a more complicated surgical procedure as well as delayed gastric emptying, so-called Roux-en-Y stasis. All surgeons recognize these issues, and their decisions on which approach to use are based on individual experience. Clinical randomized trials are very important

in providing surgeons with information to facilitate their decision-making. Ishikawa et al. [12] conducted a randomized trial and showed that B-I reconstruction was superior to R-Y in terms of shorter postoperative hospital stay. At the time it was carried out, this study was the first and most important trial comparing B-I and R-Y reconstructions, and many surgeons have referred to its results as clinical evidence. Our study should also be useful in assisting surgeons with deciding between the two procedures.

In summary, this questionnaire survey using the EORTC QLQ-C30 and DAUGS 20 scales revealed that the B-I and R-Y reconstruction approaches were nearly equal in terms of postoperative QOL and dysfunction. It is noteworthy, however, that B-I was significantly better regarding the total DAUGS 20 score during the first 6 months after surgery. The current study revealed differences in QOL and postoperative dysfunction scores between the two modes of reconstruction at various time points. More refined prospective trials with improved designs based on these results have to be proposed.

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Conflict of interest None of the authors have financial or personal conflicts of interest to disclose.

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Randomized control trials

Randomized study of clinical effect of enteral nutrition support during neoadjuvant chemotherapy on chemotherapy-related toxicity in patients with esophageal cancer

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SUMMARY

Background & aims: Enteral nutrition (EN) is provided for patients with cancer. However, Little is known about the clinical efficacy of EN support during chemotherapy in patients with cancer.
Methods: Ninety-one patients who received neoadjuvant chemotherapy (5-fluorouracil, cisplatin and adriamycin) for esophageal cancer were enrolled to receive either EN ($n = 47$) or PN ($n = 44$) at random. The primary endpoint was the incidence of chemotherapy-related toxicities during chemotherapy.
Results: Total and dietary intake calories during chemotherapy were equal in the two groups. There were no significant differences in serum albumin level and body weight change after chemotherapy between the two groups. There was no significant difference in tumor response to chemotherapy between the two groups (EN: 51%, PN: 55%, $p = 0.886$). Leukopenia and neutropenia of grade 3 or 4, defined according to the Common Toxicities Criteria of the National Cancer Institute, were significantly less frequent in the EN group than PN group (leukopenia: 17% vs 41%, $p = 0.011$, neutropenia: 36% vs 66%, $p = 0.005$). Lymphopenia and thrombocytopenia tended to be less frequent in the EN group, albeit insignificantly.
Conclusions: Compared with PN support, EN support during neoadjuvant chemotherapy reduced the incidence of chemotherapy-related hematological toxicities in patients with esophageal cancers.
The clinical trial registration number: UMIN000004483

1. Introduction

Esophageal cancer is the eighth most common incident cancer and sixth most common cause of cancer death.[1] Surgery is regarded as standard management for esophageal cancer, but the prognosis of patients who receive only surgery is poor.[2,3] To improve the survival rate in these patients, chemotherapy with or without radiotherapy followed by surgery has become one of the standard treatment strategies for esophageal cancer.[4–8] Indeed, chemotherapy is currently an important component of treatment of not only esophageal cancers but also other gastrointestinal cancers. However, chemotherapy is associated with a variety of chemotherapy-related toxicities. Bone-marrow suppression, such as leukopenia and anemia, stomatitis, appetite loss, nausea and diarrhea are frequently observed during chemotherapy, and such adverse effects sometimes force the patient to quit treatment. The efficacy of chemotherapy is usually dose-dependent, while the dose is limited by the side effects.[9] Therefore, approaches to reduce chemotherapy-related toxicities are needed, not only to relieve pain associated with the above adverse effects but also to maximize the efficacy of chemotherapy.

Recent clinical evidence has supported the benefits of enteral nutrition in cancer patients. Especially in malnourished cancer patients, enteral nutrition maintains quality of life and improves nutritional status by increasing or ensuring nutrient intake.[10–12] In patients with moderate or severe malnutrition, especially those who undergo surgery for cancer or peritonitis, perioperative enteral nutrition has been reported to reduce morbidity and mortality related to gastrointestinal surgery and reduce the duration of hospitalization.[13–17] In addition to its usefulness in patients on surgery, enteral nutrition during radiotherapy significantly enhances dietary intake, prevents weight loss and promotes adherence to radiotherapy.[11,17–20] However, for patients with

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cancers who undergo chemotherapy, effect of enteral nutrition during chemotherapy on chemotherapy-related toxicities or response to chemotherapy has not been established. In esophageal cancer, patients sometimes are malnourished at the initial diagnosis, and cisplatin-based chemotherapy which is a standard chemotherapy for esophageal cancer often cause the reduced dietary intake due to cisplatin-induced anorexia. Therefore, during cisplatin-based chemotherapy for patients with esophageal cancer, enteral nutrition support may be beneficial.

The present study was designed to examine whether enteral nutrition during chemotherapy help reduce chemotherapy-related toxicities. Among the various enteral nutrients, we focused on omega-3 fatty acids-rich nutritional supplements. Omega-3 fatty acids have been reported to have anti-inflammatory effects, improve immune function, and reduce intestinal damage caused by anti-cancer agents.[21–26] The study compared enteral nutritional support with parenteral nutrition during chemotherapy for advanced esophageal cancer. All chemotherapy-related toxicities were evaluated in both groups.

2. Materials and methods

2.1. Patients

Patients were entered into the study according to the following eligibility criteria: 1) previously untreated and histopathologically-confirmed thoracic esophageal cancer; 2) clinical stage IIA, IIB, III or IV with distant node involvement; 3) age ≥20 or ≤80 years; 4) an Eastern Cooperative Oncology Group performance status (PS) of 0–2; 5) adequate hepatic, renal and bone-marrow reserve (leukocyte count > 3500/mm^3, hemoglobin > 10 g/dl, platelet count > 100,000/mm^3, AST and ALT not higher than twice the normal levels; total serum bilirubin < 3.0 mg/dl; and creatinine level <1.3 mg/dl; 6) ability of oral intake; 7) oral or written informed consent obtained before randomization. Patients were ineligible if they had severe stenosis of esophagogastro-intestinal tract or they had uncontrolled diabetes.

In this study, all patients were staged before treatment according to the criteria of the International Union Against Cancer (UICC). Pretreatment clinical staging was based on endoscopy, computed tomography (CT) scans of the neck, chest and the upper abdomen as continuous 5 mm thick slices and, if at all possible, positron emission tomography (PET) scan. Lymph nodes were diagnosed as metastasis-positive on CT scan if they were greater than 1.0 cm in maximum transverse diameter. Lymph nodes visible but smaller than 1.0 cm on the long axis on CT scan were regarded as metastasis-positive only if focal prominent 18-fluorodeoxy glucose (FDG) uptake, compared with normal mediastinal activity, was detected on the PET scan.

The study protocol was approved by the Human Ethics Review Committees of Osaka University Graduate School of Medicine, Osaka Medical Center for Cancer and Cardiovascular Diseases and Kinki University.

2.2. Study design and treatment

Patients were randomly assigned to either the enteral nutrition (EN) group or parenteral nutrition (PN) group. The sizes of the groups were balanced according to institution, gender and serum albumin level. A coordinating center (section of the Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University) generated the treatment allocation codes using a computer generated randomization table.

In both groups, the enrolled patients received neoadjuvant chemotherapy consisting of cisplatin, adriamycin and 5-fluorouracil (5-FU). Cisplatin was administered at 70 mg/m^2, adriamycin at 35 mg/m^2 by rapid intravenous infusion on day 1; and 5-FU at 700 mg/m^2 administered by continuous intravenous infusion on day 1 through day 7.[27] Supportive therapy and prophylaxis against expected side effects was provided. Antagonists of 5-HT3 receptor were routinely administered prophylactically at day1–7 in both groups. Adequate hydration was ensured before and after cisplatin infusion. Additional antiemetics or steroid preparation were recommended in case of grade-3 or higher anorexia, nausea, and vomiting by the toxicity grading criteria of the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Granulocyte-stimulating factor (G-CSF) was used for febrile neutropenia when deemed necessary. Two courses of chemotherapy were provided, separated by a 4-week interval, except when the tumor did not show any sign of significant regression after the first course of chemotherapy. Patients underwent surgery 3–5 weeks after the completion of neoadjuvant chemotherapy only if complete tumor resection was considered possible.

2.3. Parenteral or enteral nutrition support

In patients assigned to the EN group, omega-3 fatty acid-rich nutritional supplements (Racol, Otsuka Pharmaceuticals, Tokyo, Japan) at 600 ml/day (600 kcal/day) were provided. The composition of the nutritional supplements was 4.38 g protein, 2.23 g lipid (omega-3 fatty acids: omega-6 fatty acids = 1: 3) and 16.62 g carbohydrate in 100 ml volume. Omega-3 fatty acid-rich nutritional supplement was administered from 3 days before the start of chemotherapy to 7 days after completion of chemotherapy (for 17 days). Basically, patients drank the supplement or it was administered through a trans-nasal feeding tube when oral intake was not possible due to chemotherapy-related toxicities such as nausea and stomatitis. During that time, patients took oral diet arbitrarily and when oral intake decreased, parenteral nutrition support was instituted to compensate for the reduced calories through oral intake.

In patients assigned to the PN group, parental nutrition support at 600 kcal/day was provided from 3 days before the start of chemotherapy to 7 days after the completion of chemotherapy (for 17 days). The composition of the intravenous infusion which was provided as basal parenteral nutrition support was 130.0 g glucose, 50 mEq Na, 22 mEq K, 50 mEq Cl, and 20.0 g free amino acids in 1000 ml volume. As in the EN group, patients took oral diet arbitrarily and when oral intake decreased, parenteral nutrition support was instituted to compensate for the reduced calories through oral intake. Thus, the treatment protocol was arranged to maintain the total intake calories during the study period in both groups (Fig. 1). Food intake calories based on the food weight measured by the patient, including standard meal and extra foods, were calculated by dietitians using a calorimeter. In both groups, the desired total intake calories was set at 40–50 kcal/kg/day.

2.4. Evaluation of response to chemotherapy

The clinical response was categorized according to the following criteria [based on the Response Evaluation Criteria in Solid Tumors (RECIST) guideline and the criteria of the Japanese Society for Esophageal Diseases].[27,28] A complete response (CR) was defined as clinical complete regression of the disease. A CR of the primary tumors was determined when the tumors disappeared on CT scan and/or PET scan and endoscopy. If further ulceration and presence of cancer cells in biopsy samples was confirmed by endoscopy, the case was excluded from the CR group. A partial response (PR) was defined as more than 30% reduction in maximum transverse diameter of the primary tumor, on the CT scan. Progressive disease (PD) was defined as more than 20% increase in maximum transverse diameter of the

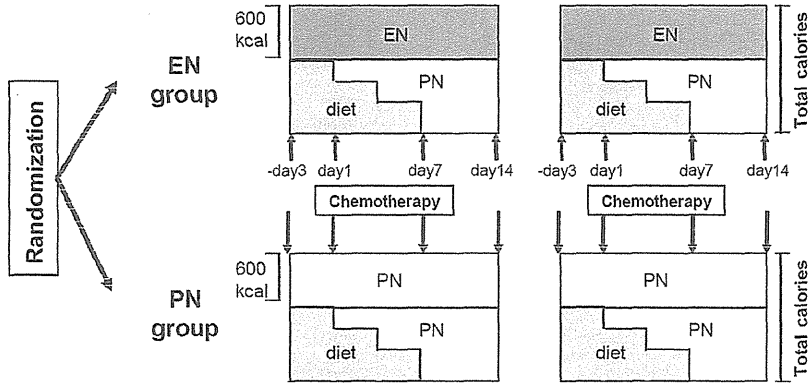

Fig. 1. Treatment schedule.

primary tumor or the appearance of new lesions. Cases that did not meet the criteria of PR and PD were defined as stable disease (SD).

The degree of histopathological tumor regression in surgical specimens was classified into five categories.[27–29] The percentage of viable residual tumor cells within the total cancerous tissue was assessed as follows: Grade 3, no viable residual tumor cells; Grade 2, less than 1/3 residual tumor cells; Grade 1b, 1/3–2/3 residual tumor cells; Grade 1a, more than 2/3 residual tumor cells; Grade 0, no significant response to chemotherapy.

2.5. Evaluation of chemotherapy-related toxicities and blood sampling

Toxicity was evaluated and scored by the most severe toxicity in the first cycle by toxicity (days 1–28) grading criteria of CTCAE version 3.0. Blood examination was performed at least once a week during the course of chemotherapy. Non-hematological adverse events such as nausea, vomiting, diarrhea and stomatitis were assessed daily during the entire course of chemotherapy. Dose modifications in the second cycle were based on treatment-related adverse events recorded in the first cycle. The dose of cisplatin and adriamycin was reduced by 20% for grade 4 neutropenia lasting for more than 7 days, febrile neutropenia grade 3 or higher, and thrombocytopenia grade 3 or higher.

The lipid profile and fatty acids in blood were examined before treatment and at days 14 and 42. The ratio of omega-3 fatty acids to omega-6 fatty acids was defined as the ratio of eicosapentaenoic acid (EPA) to arachidonic acid (AA).

2.6. Statistical analysis

The primary endpoint was frequency of chemotherapy-related adverse effects. The secondary endpoints were nutritional status including body weight and, serum albumin. The rate of grade 3 or 4 toxicities such as leukopenia, neutropenia and nausea in the PN group was expected to be 50%, based on our previous results.[27] We planned initially to recruit 90 patients, a number that would allow detection of 30% decrease in the incidence of grade 3 or 4 toxicities in the EN group, with two-sided alpha error of 0.05 and statistical power of 80%.

The baseline characteristics and response to chemotherapy were compared using chi-square test or Mann–Whitney *U* test. Comparison of intake calories between the treatment groups was tested by the Student *t*-test, and comparison of adverse effects between the groups were evaluated by the Mann–Whitney *U* test. The Cox proportional hazards regression model was used to identify variables significantly associated with occurrence of chemotherapy-related neutropenia. Continuous variables were expressed as mean ± standard deviation unless otherwise stated. *P* values less than 0.05 were considered to indicate statistical significance. All analyses were carried out using the StatView software package version 5.0 (SAS Institute Inc., Cary, NC).

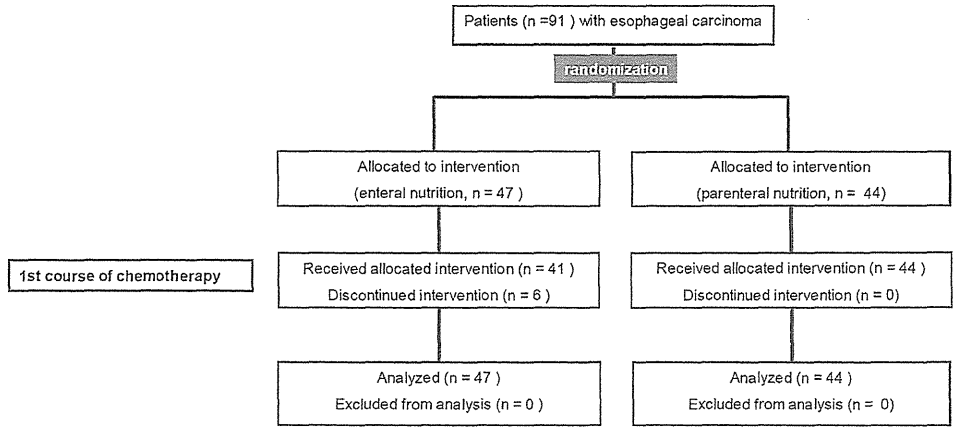

Fig. 2. CONSORT diagram.

3. Results

3.1. Patient characteristics

During the period from December 2007 to February 2010, 91 patients who received neoadjuvant chemotherapy for esophageal cancer were enrolled in this study, and 47 patients were randomly assigned to the EN group and 44 patients to the PN group (Fig. 2). Table 1 summarizes the pretreatment characteristics of all 91 patients enrolled in this study. The baseline prognostic variables, such as age, gender, body mass index, cT, cN, cM and cStage were well balanced between the two groups.

3.2. Calorie intake and nutritional status

Dietary intake calories during chemotherapy were almost similar between the EN and PN groups (Table 2). Among the 47 patients of the EN group, EN supplementation was discontinued during the first course of chemotherapy in 6 patients who refused to continue EN treatment because of adverse events such as nausea and vomiting. In the EN group, patients consumed an average of 530 kcal of omega-3 fatty acid-rich nutritional supplements per day. Thus, the ratio of omega-3 to omega-6 fatty acids on day 14 was significantly higher in the EN group than PN group (Average value of EPA and AA in EN group was 2.1 % and 5.7 % of total fatty acids before treatment and 1.6 % and 5.4 % of total fatty acids at day 14. Average value of EPA and AA in PN group was 2.1 % and 5.9 % of total fatty acids before treatment and 1.3 % and 5.6 % of total fatty acids at day 14.) (Fig. 3). On the other hand, the calorie content of administered parenteral nutrition was higher in the PN group than EN group. Thus, total intake calories during chemotherapy were almost similar between the EN and PN groups.

There were no significant differences in serum albumin level and body weight at day 14 between the two groups (Table 2).

3.3. Compliance and response to chemotherapy

Among the 47 patients of the EN group, 5 received the first course of chemotherapy only; because of renal dysfunction in one patient, no apparent tumor regression in the remaining four during that period. Among the 44 patients of the PN group, 5 received the first course of chemotherapy only; because of renal dysfunction in one patient, no apparent tumor regression in the remaining four during that period. The drug dose was reduced in the second course of chemotherapy in the 5 patients of the EN group and 4 patients of the PN group.

In each group, 2 patients achieved clinical complete response (4.3% in EN group and 4.5% in PN group, Table 3). The response rate to chemotherapy was not different between the two groups (EN group: 51%, PN group: 55%). Among the 47 patients of the EN group, 44 (including 3 patients who received chemoradiotherapy after neoadjuvant chemotherapy) underwent surgical resection while 3 patients did not undergo surgery due to bone metastasis in one patient, chemotherapy-related failure in one and tumor growth in one. In the PN group, 40 of 44 patients, including one who received chemoradiotherapy after neoadjuvant chemotherapy, underwent surgical resection while 4 patients did not undergo surgery due to bone metastasis in two patients, and tumor growth in two. The histopathological response after neoadjuvant chemotherapy followed by surgery was almost similar between the two groups.

Table 1
Characteristics of patients.

		EN group	PN group	*P* value
n		47	44	
Age		62.4	63.2	0.643
Gender	Male	34	35	0.470
	Female	13	9	
Body mass index		21.3	20.9	0.550
Histology	SCC	47	42	0.139
	Others	0	2	
Tumor depth	cT1	1	4	0.650
	cT2	13	8	
	cT3	26	21	
	cT4	7	11	
Lymph node involvement	cN0	4	4	0.922
	cN1	43	40	
Distant metastasis	cM0	32	24	0.185
	cM1	15	20	
Stage	Stage II	13	9	0.199
	Stage III	19	15	
	Stage IV	15	20	

EN: enteral nutrition group, PN: parenteral nutrition group, SCC: squamous cell carcinoma.

Table 2
Food intake calories per day for 17 days (from 3 days before the start of chemotherapy to 7 days after the completion of chemotherapy) and nutritional status at day 14.

	EN group ($n = 47$)	PN group ($n = 47$)	*P* value
Enteral nutrition (kcal)	530 ± 147	0	<0.0001
Parenteral nutrition (kcal)	434 ± 328	925 ± 311	<0.0001
Dietary intake calories (kcal)	942 ± 436	843 ± 439	0.286
Total intake calories (kcal)	1906 ± 322	1768 ± 303	0.211
Serum albumin at day 14 (mg/dl)	3.3 ± 0.7	3.2 ± 0.6	0.282
Change in body weight at day 14 (%)	99.4 ± 3.0	99.9 ± 3.2	0.375

Data are mean ± standard deviation.
EN: enteral nutrition group, PN: parenteral nutrition group.

3.4. Chemotherapy-related adverse events

Data on 47 patients of the EN group including 6 patients who could not continue EN supplementation during chemotherapy and 44 patients of the PN group were analyzed for adverse events during the first course of neoadjuvant chemotherapy. Leukopenia and neutropenia were significantly less frequent in the EN group than the PN group (Table 4). Lymphopenia and thrombocytopenia tended to be less common in the EN group, compared with the PN group, although this difference did not reach statistical significance. On the other hand, there were no significant differences in non-hematological side effects such as nausea, diarrhea and stomatitis, between the two groups, with the exception that elevated

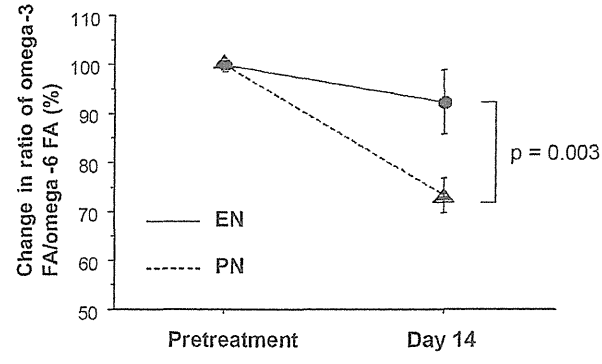

Fig. 3. Comparison of the ratio of omega-3 fatty acids to omega-6 fatty acids in the serum at day 14 between the enteral group and parenteral group. The ratio of omega-3 fatty acids (FA) to omega-6 fatty acids at day 14 was significantly higher in the enteral group in parenteral group.

Table 3
Effect of enteral nutrition support on response to chemotherapy.

	EN group	PN group	*P* value
Response to chemotherapy			
CR	2	2	0.746
PR	22	22	
SD/PD	23	20	
Surgery			
yes	44	40	0.628
no	3	4	
Histopathological tumor regression			
Grade 3	2	1	0.428
Grade 2	4	4	
Grade 1b	7	11	
Grade 0–1a	31	24	

EN: enteral nutrition group, PN: parenteral nutrition group.

creatinine level was less frequent in the EN group than the PN group.

We performed logistic regression analysis to identify significant factors influencing the occurrence of grade3/4 neutropenia. Multivariate analysis revealed that dietary intake calories and enteral nutrition support were significant factors for occurrence of grade 3–4 neutrpenia (Table 5). Next, we analyzed the effect of enteral nutrition support on occurrence of grade3/4 neutropenia in subgroups, more than 1000 kcal/day of dietary intake or less than 1000 kcal/day of dietary intake. Subgroup analysis showed that enteral nutrition support during chemotherapy decreased occurrence of grade3/4 neutropenia in patients who consumed less than 1000 kcal/day of dietary intake, whereas enteral nutrition support did not have a significant influence on occurrence of grade3/4 neutopenia in patients who consumed more than 1000 kcal/day of dietary intake (Fig. 4).

4. Discussion

The use of enteral nutrition support is indicated for malnourished patients with cancer, but the clinical efficacy of EN support during chemotherapy in patients with cancer has not been established. In this study, we demonstrated that EN support during chemotherapy for patients with esophageal cancer reduces chemotherapy-related hematological adverse events, in particular, leukopenia and neutropenia, although it affected neither tumor response to chemotherapy nor body weight change during chemotherapy.

Several studies have shown the clinical efficacy of perioperative EN support in patients with cancer scheduled for surgery,[30–32] but little information is available on the clinical efficacy of EN support during chemotherapy. Klein and Koretz[33] analyzed 7 randomized controlled trials that examined the use of EN support in patients receiving chemotherapy. They concluded that these studies did not allow full assessment due to differences in the formula composition, timing and duration of nutrition therapy. In addition, several studies were of low quality because either the sample size was small or EN support was not properly provided to patients randomized to receive EN therapy, and no obvious therapeutic benefit was noted with respect to survival, tumor response, or chemotherapy-related toxicity. Current results clearly showed that EN support during chemotherapy reduced the incidence of chemotherapy-related hematological adverse events such as leukopenia and neutropenia. Recently, as chemotherapy regimen which is used in the treatment for gastrointestinal cancers including esophageal cancer and gastric cancer become more powerful, hematological toxicities such as leucopenia and neutropenia become more common while the response rate is getting higher.[34,35] Therefore, we think that current result that EN support during chemotherapy may have the potential of reducing hemoatological toxicities is of clinical importance in the treatment for esophageal cancer.

One possible reason of positive result in this study is that we designed the current study to examine the effect of EN support in combination with neoadjuvant chemotherapy after ensuring the inclusion of two otherwise homogeneous groups with respect to patient background. Neoadjuvant setting may allow this study to make a significant difference in chemotherapy-related toxicities between enteral nutrition and parenteral nutrition. Another possible

Table 4
Adverse events.

		Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	*P* value
(A) *Hematological adverse events*							
Leukopenia	EN	17	12	10	8	0	0.004
	PN	8	8	10	13	5	
Neutropenia	EN	19	5	6	10	7	0.007
	PN	8	3	4	17	12	
Lymphopenia	EN	18	15	9	5	0	0.068
	PN	11	11	15	6	1	
Thrombocytopenia	EN	35	12	0	0	0	0.061
	PN	26	12	4	2	0	
(B) *Non-hematological adverse events*							
AST increased	EN	37	10	0	0	0	0.094
	PN	28	14	2	0	0	
ALT increased	EN	31	11	3	0	0	0.215
	PN	25	16	2	1		
Creatinine increased	EN	38	8	1	0	0	0.042
	PN	27	15	2	0	0	
Nausea	EN	3	13	14	17	0	0.565
	PN	4	11	8	21	0	
Vomiting	EN	25	11	10	1	0	0.733
	PN	24	13	5	2	0	
Diarrhea	EN	22	17	5	3	0	0.095
	PN	14	17	8	5	0	
Stomatitis	EN	12	16	12	7	0	0.560
	PN	9	14	15	6	0	

EN: enteral nutrition group, PN: parenteral nutrition group.

Table 5
Multivariate analysis for occurrence of grade3/4 neutropenia.

Variables		HR	95% CI	*P* value
Gender	Female	1.35	0.51–3.79	0.684
Age	≥70	1.61	0.51–4.62	0.447
Body mass index	<18.5	1.04	0.32–2.91	0.945
Albumin	<3.5 mg/dl	1.30	042–4.05	0.646
Tumor stage	Stage IV	0.54	0.20–1.48	0.232
Oral intake calories	<1000 kcal	2.23	1.01–5.32	0.048
Enteral nutrition support	Performed	0.28	0.11–0.69	0.006

HR: hazard ratio, 95% CI: 95% confidence interval.

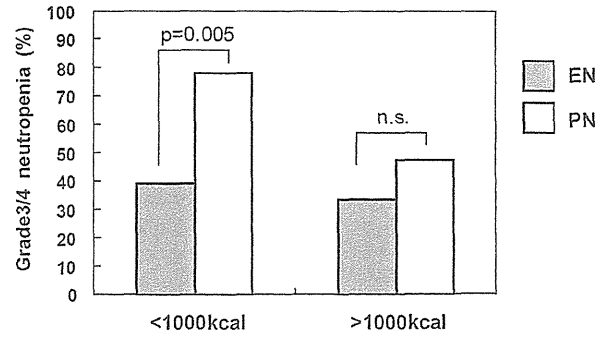

Fig. 4. The incidence of grade3/4 neutropenia in patients who consumed less than 1000 kcal/day of dietary intake (left), and those who consumed more than 1000 kcal/day of dietary intake (right). EN: enteral nutrition, PN: parenteral nutrition.

reason of current positive result is that we conducted the current study for patients who received cisplatin-based chemotherapy. Among various anti-cancer drugs, cisplatin is well-known to be one of the most highly emetic drugs. Patients who receive cisplatin-based chemotherapy often can not take adequate nutrition orally due to cisplatin-induced nausea, and nutrition support during chemotherapy is required for those patients. This decreased dietary intake caused by cisplatin-based chemotherapy may be responsible for current result that enteral nutrition support reduced chemotherapy-related hematological toxicities. Indeed, in subgroup analysis, enteral nutrition support during chemotherapy decreased occurrence of grade3/4 neutropenia in patients who consumed less than 1000 kcal of dietary intake whereas enteral nutrition support did not have a significant influence on occurrence of grade3/4 neutopenia in patients who consumed more than 1000 kcal of dietary intake.

It is commonly believed that poor nutritional status, such as body weight loss, is associated with increased treatment-related adverse reactions.[36] However, in this study, the indicators used for nutritional status such as body weight and serum albumin level were almost similar during chemotherapy between the EN and PN groups. The reason for this finding may be related to the study design; both groups received similar total intake calories during therapy. In fact, there was no significant difference in dietary intake calories and total intake calories between the two groups. In the PN group, however, the intake calorie of EN supplementation in the EN group was equal to that provided to patients on parenteral nutrition. The differences in the incidences of hematological adverse events between the two cannot be due to differences in nutritional status between the two, but probably due to differences in the type of intake calories, enteral or parenteral. In fact, in the 6 patients of the EN group who could not continue taking EN supplementation, the frequencies of leukopenia and neutropenia of grade 3 or 4 were 33% and 50%, which were almost comparable to those in patients of the PN group.

In this study, enteral nutrition during chemotherapy did not affect tumor response to chemotherapy. Many previous studies investigated whether nutrition support in patients with cancer undergoing chemotherapy or radiotherapy affect tumor response to treatment or patients survival. The majority of those studies did not show a positive effect for nutrition support on survival or tumor response, although nutrition support significantly increased energy intake and reduced therapy-associated weight loss.[11,12,17–20,33] Our results of tumor response showing no improvement with EN support is consistent with the above previous studies. Regarding effect of enteral nutrition support on patient survival, we could not conclude whether EN support improves patient survival or not mainly because of the short follow-up time.

One limitation of the present study is that the possibility that the reduced toxicity in EN group was due to the omega-3 fatty acids, which were abundantly present in enteral nutritional supplement used in this study, cannot be ruled out. The treatment protocol was arranged to equalize intake calories of nutritional support (enteral or parenteral) between EN group and PN group, but the composition of EN support and PN support was not identical. While EN support contains less carbohydrate and less amino acids than PN support, EN support contain more fatty acids including omega-3 fatty acids. In mice, omega-3 fatty acids are reported to reduce the chemotherapy-related toxicities including intestinal damage[25,26] and hematological toxicities.[37] Moreover, one recent study showed that nutritional intervention with fish oil appear to prevent deterioration of weight and muscle mass during chemotherapy in patients with non-small lung cancer.[38] Thus, omega-3 fatty acids in enteral nutritional supplement may contribute to the reduced incidence of hematological toxicities. In fact, the ratio of omega-3 fatty acids to omega-6 fatty acids at day 14 was significantly higher in patients of the EN group, compared to those of the PN group. To examine whether enteral nutrition support or omega-3 fatty acids supplementation is important in terms of reducing chemotherapy-related hematological toxicities, we now plan to conduct prospective randomized study comparing enteral nutrition containing omega-3 fatty acids with enteral nutrition without omega-3 fatty acids in patients who receive cisplatin-based chemotherapy for esophageal cancer.

In conclusion, the present study demonstrated that enteral nutritional support using omega-3 fatty acids-rich nutritional supplements during neoadjuvant chemotherapy reduced chemotherapy-related hematological toxicities such as leukopenia and neutropenia without affecting tumor response to chemotherapy in patients with esophageal cancer. Further studies are required to determine the mechanism of action of EN support on chemotherapy-related hematological toxicities.

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Statement of authorship

The authors' responsibilities were as follows: HM and YD: design of the study, collection and analysis of data, and writing of the manuscript; MY, TY, RH, MY, EH, MM, OS, KT and MM: design of the study, collection and analysis of data. All authors read and approved the final manuscript.

Conflict of Interest

There is no conflict of interest from authors related this study.

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Clinical Relevance of Induction Triplet Chemotherapy for Esophageal Cancer Invading Adjacent Organs

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Background and Objectives: There is no consensus on treatment for esophageal cancer invading adjacent organs (T4), but induction multidrug chemotherapy may be a beneficial, especially when surgery is considered as adjuvant treatment.
Methods: We classified 169 patients with T4 esophageal cancer without distant metastasis into those undergoing chemotherapy using cisplatin and 5-FU (CF) plus adriamycin or CF plus docetaxel (79 patients) and those undergoing chemoradiotherapy using CF (90 patients). For the former group, chemoradiation was subsequently applied when surgical resection was not indicated.
Results: Thirty-four patients in the chemotherapy group (43.0%) received chemoradiotherapy following chemotherapy. Although the response rate tended to be higher in the chemoradiotherapy group, there was no significant difference in the response rate between the groups (63.3% vs. 68.9%). Esophageal perforation during treatment was more frequent among the chemoradiotherapy group than the chemotherapy group (16.7% vs. 6.3%, $P = 0.0379$). The rate of surgical resection was consequently higher for the induction chemotherapy group compared to the chemoradiotherapy group (72.1% vs. 45.6%, $P = 0.0005$).
Conclusions: Induction triplet chemotherapy reduced esophageal perforation and increased the resectability of T4 esophageal cancers by combining second-line chemoradiotherapy. This strategy might increase the chance of curative resection for patients with T4 esophageal cancer.
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KEY WORDS: **esophageal cancer; chemotherapy; chemoradiotherapy; adjacent organ; T4**

INTRODUCTION

Esophageal cancer is one of the most virulent of all gastrointestinal cancers. Esophagectomy is the traditional treatment for locoregional esophageal cancer [1,2], although the indication for such surgery is often limited because of the advanced stage of disease at the time of diagnosis. In particular, esophageal cancers sometimes invade adjacent structures such as trachea, left main bronchus, and descending aorta, with the reported incidence of locally far advanced tumors (T4) invading adjacent organs being 10–30% among thoracic esophageal cancers [3–8]. However, a consensus on the standard treatment for T4 esophageal cancer remains difficult to achieve.

Many investigators believe that definitive chemoradiotherapy without surgery is suitable for patients with T4 esophageal cancer [9–16], with reported rates of complete response (CR) at 25–32% [9,12,13]. However, other studies have suggested that chemoradiotherapy followed by surgery improves survival rate in patients with T4 esophageal cancer [3,6,17–20]. In those reports, the rate of curative resection was 32–78% and patients who underwent curative resection showed significantly better survival [3,6,17,19,20]. Thus, chemoradiotherapy as the initial treatment for T4 esophageal cancer is widely accepted as appropriate, irrespective of neoadjuvant, or definitive settings.

Induction chemotherapy has emerged as an alternative initial treatment for T4 esophageal cancer [7]. Down-staging was achieved in 62% of patients with T4 tumors and of these, 52% underwent surgical resection following first-line chemotherapy comprising a standard regimen of cisplatin and 5-fluorouracil (5-FU; CF) [7]. Recent studies also suggested that induction chemotherapy using aggressive regimens consisting of multiple anti-cancer drugs such as 5-FU, cisplatin, and epirubicin, or 5-FU, cisplatin, and docetaxel could be more effective not only for controlling micrometastasis, but also for local tumor control in patients with advanced esophageal cancer [21,22]. Moreover, induction chemotherapy may improve local tumor control by combining with chemoradiotherapy as a second-line therapy for patients with locally advanced esophageal cancer.

In our hospital, induction chemotherapy or chemoradiotherapy was administered to patients with T4 esophageal cancer, followed by surgical resection when down-staging was achieved by the induction therapy. The present study was designed to determine whether induction chemotherapy using triplet anti-cancer drugs in combination with second-line chemoradiotherapy is comparable or superior to chemoradiotherapy using standard chemotherapy consisting of CF in terms of local tumor control and resectability rate.

MATERIALS AND METHODS

Patient Eligibility

From March 1996 to December 2009, 214 patients with esophageal cancer invading adjacent structures (T4 tumors) were treated at The Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University. During the same period, 689 patients with esophageal cancer underwent surgery in our institute. Among 214 patients with T4 esophageal cancer, 169 patients who had

The authors declared that they have no conflict of interest.

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thoracic esophageal cancers invading adjacent structures without distant organ metastasis were included in this study; 11 patients with distant organ metastasis, 3 patients with esophageal fistulae at initial diagnosis, 25 patients whose tumors are located at the cervical esophagus, and 6 patients who could tolerate neither chemotherapy nor chemoradiotherapy because of bad general status were excluded. Patients who had cervical lymph node metastasis or celiac lymph node metastasis (M1lym) were eligible. All 169 patients were histologically confirmed as having squamous cell carcinoma of the esophagus. Of these, 90 patients received chemoradiotherapy and 79 patients received induction chemotherapy as their initial treatment.

All study patients were staged before and after surgery according to the criteria of the International Union Against Cancer (UICC).[23] Pretreatment clinical staging was based on esophageography, endoscopy, and computed tomography (CT) of the neck, chest, and upper abdomen using continuous 5-mm-thick slices. Bronchoscopy was performed when tracheobronchial involvement was suspected. From March 2000, positron emission tomography (PET) was also used in our facility for clinical staging where possible. The diagnostic criteria for T4 tumors were as described previously [13,20,24,25]. Briefly, patients with tumors extending into the lumen or causing deformity of the airway at the tracheobronchial tree were diagnosed as having tracheobronchial invasion. If the fat plane in the triangular space between the esophagus, aorta, and spine was obliterated or if a tumor mass shadow was observed between the aorta and spine, or if the degree of direct contact between the tumor and aorta exceeded 90° on CT, aortic invasion was deemed to be present. The tumor length was measured by the maximum transverse diameter on CT cross-section.

All patients were <80 years of age, had adequate cardiac, hepatic, renal and bone marrow reserve, and could tolerate both the planned chemotherapy or chemoradiotherapy and the following surgical procedures. The Human Ethics Review Committee of Osaka University Graduate School of Medicine approved the protocol of this retrospective study and each subject provided signed consent.

Treatment Protocols

The preoperative chemoradiotherapy regimen in our hospital consisted of simultaneous radiation with administration of CF as described previously [26]. The 5-FU was administered by continuous intravenous infusion at a dose of 400 mg/m^2 in combination with cisplatin at 10 mg/m^2 administered by drip infusion for 5 days per week. External-beam radiation therapy was administered by a 10-MV X-ray linear accelerator with 2 Gy per fraction per day and five fractions per week for 4–6 weeks, for a total dose of 40–60 Gy.

From March 1996 to June 2008, induction chemotherapy in our hospital consisted of cisplatin, adriamycin, and 5-FU (ACF). The cisplatin was administered at 70 mg/m^2, adriamycin at 35 mg/m^2 by rapid intravenous infusion on day 1, and 5-FU at 700 mg/m^2 administered by continuous intravenous infusion on days 1 through 7. Two courses of chemotherapy were used, separated by a 4-week interval [27]. From July 2008 to December 2009, induction chemotherapy in our institute consisted of cisplatin, docetaxel, and 5-FU (DCF). The cisplatin was administered at 70 mg/m^2, docetaxel at 70 mg/m^2 by rapid intravenous infusion on day 1, and 5-FU at 700 mg/m^2 administered by continuous intravenous infusion on days 1 through 5. Two courses of chemotherapy were used, separated by a 3-week interval. Consequently, among 79 patients in the induction chemotherapy group, 62 patients received ACF and 17 patients received DCF therapy. If T4 invasion was not relieved by induction chemotherapy alone, the additional chemoradiotherapy was performed. Second-line chemoradiotherapy involved the same treatment protocol as first-line chemoradiotherapy using CF. In principle, when T4 invasion was relieved by chemotherapy and/or chemoradiotherapy, and complete tumor resection was regarded as possible, surgical resection was performed.

Evaluation of Clinical Response

After completion of the induction chemotherapy and/or chemoradiotherapy, all patients were restaged by CT, endoscopy, and PET to evaluate the clinical response to chemoradiotherapy. The response was categorized based on the World Health Organization response criteria for measurable disease and the criteria of the Japanese Society for Esophageal Diseases [28]. A CR was defined as complete regression of disease based on CT scan and/or PET scan and endoscopy. The patient was not considered as achieving a CR when persistent ulceration and/or presence of cancer cells in biopsy samples were confirmed on endoscopy [13]. Partial response (PR) was defined by >50% reduction in the size of the primary tumor and lymph node (LN) metastasis, as confirmed by CT and endoscopy. Progressive disease (PD) was defined by >25% increase in the size of the primary tumor or the appearance of new lesions. Cases that did not meet the criteria of PR or PD were defined as stable disease (SD) [13,28]. The histopathological findings were classified according to the UICC TNM classification. The degree of histopathological tumor regression in the surgical specimens was classified into five categories [26,28]. The extent of viable residual carcinoma at the primary site was assessed semiquantitatively, based on the estimated percentage of viable residual carcinoma in relation to the macroscopically identifiable tumor bed that was evaluated histopathologically. The percentage of viable residual tumor cells within the entire cancerous tissue was assessed as follows: Grade 3, no viable residual tumor cells (pCR); Grade 2, <1/3 residual tumor cells; Grade 1b, 1/3–2/3 residual tumor cells; Grade 1a, more than 2/3 residual tumor cells; Grade 0, no significant response to chemoradiotherapy [26,28].

Statistical Analysis

All data are expressed as mean ± SD. Student's *t*-test, Mann–Whitney's *U*-test, and the chi-square test were used to compare the baseline characteristics of the treatment group, and to compare the response to therapy and recurrence pattern between the two groups. Overall survival was calculated from the date of induction chemotherapy or chemoradiotherapy to the occurrence of the event or to the last known date of follow-up. Actual survival was calculated by the Kaplan–Meier method and evaluated statistically by the log-rank test. The Cox proportional hazards regression model was used to analyze the simultaneous influence of prognostic factors. A *P*-value <0.05 was considered to reflect statistical significance. These analyses were carried out using the StatView J5.0 software package (Abacus Concepts, Berkeley, CA).

RESULTS

Characteristics of Patients and Subsequent Therapy

Table I lists the pretreatment characteristics of all 169 patients. There was no significant difference in age, tumor location, tumor length on CT, or organ invaded by the tumor. T4 organs other than trachea and aorta were as follows: five liver, four pancreas, three lung, two subclavian artery, one pericardium, and one liver and diaphragma in the induction chemotherapy group; two lung, one liver, one subclavian artery, one pericardium, and one liver and diaphragma in the chemoradiotherapy group. Lymph node metastasis and distant lymph node metastasis such as cervical nodes and celiac artery nodes were more frequently reported in the induction chemotherapy group than in the chemoradiotherapy group.

In the induction chemotherapy group, 41 of the 79 patients underwent subsequent surgical and another 34 patients received chemoradiotherapy because the T4 invasion was not relieved by induction chemotherapy alone. The remaining 4 patients underwent palliative treatment because of lung metastasis in two cases, bone metastasis in

TABLE I. Characteristics of 169 Patients With T4 Tumors and No Distant Metastasis

	Total	Induction chemotherapy	Induction CRT	*P* value
n	169	79	90	
Age (years)[a]	62.6 ± 8.1	62.2 ± 8.7	63.0 ± 7.6	0.8676
Gender				
Male	144 (85)	68 (86)	76 (84)	0.7657
Female	25 (15)	11 (14)	14 (16)	
Tumor location				
Upper third	65 (38)	28 (35)	37 (41)	0.1816
Middle third	77 (46)	34 (43)	43 (48)	
Lower third	27 (16)	17 (22)	10 (11)	
Tumor length on CT cross-section (mm)[a]	39.9 ± 12.9	40.6 ± 13.8	39.1 ± 11.8	0.4398
T4 organ				
Trachea	107 (63)	47 (60)	60 (66)	0.0707
Aorta	30 (18)	12 (15)	18 (20)	
Trachea + aorta	10 (6)	4 (5)	6 (7)	
Others	22 (13)	16 (20)	6 (7)	
cN				
cN0	36 (21)	9 (11)	27 (30)	0.0032
cN1	113 (79)	70 (89)	63 (70)	
cM				
cM0	111 (66)	41 (52)	70 (78)	0.0004
cM1lym	58 (34)	38 (48)	20 (22)	

CRT, chemoradiotherapy.
[a]Data are mean ± SD.

one case, and worsening of general condition in the other patient after induction chemotherapy. Among the 34 patients who underwent induction chemotherapy followed by chemoradiotherapy, 16 patients underwent subsequent surgical resection, while in the remaining 18 patients, 11 had tumors regarded as unresectable, 5 patients experienced esophageal perforation, and 2 patients refused surgical resection after achieving CR.

In the chemoradiotherapy group, 39 of the 90 patients (43.3%) underwent subsequent surgical resection. The remaining 51 patients did not receive surgical resection due to unresectable tumors in 20 patients, esophageal perforation in 15 patients including 1 patient who achieved CR clinically, developing distant organ metastasis in 3 patients, and refusing surgical resection for potentially resectable tumors in 11 patients including 8 patients who achieved CR (Fig. 1).

Clinical Response and Surgical Resection

On completion of the entire induction treatment including any secondary chemoradiotherapy, clinical response was evaluated and indication for surgical resection was determined. There was no significant difference in the response rate between the two groups (63.3% for induction chemotherapy vs. 68.9% for chemoradiotherapy, $P = 0.4425$), although the response rate in patients who received chemotherapy alone in the induction chemotherapy group was relatively low at 48.1%. Within the induction chemotherapy group, response rate to ACF was 45.2% (28/62 patients) and that to DCF was 58.8% (10/17 patients). CR rate was significantly higher in the chemoradiotherapy group compared with the induction chemotherapy group (17.8% vs. 3.8%, $P = 0.0041$). However, esophageal perforation during treatment occurred in 15 of 90 patients (16.7%) in the chemoradiotherapy group compared to only 5 of 79 patients (6.3%) in the induction chemotherapy group ($P = 0.0379$, Table II). Especially in induction chemotherapy alone, esophageal perforation occurred in only 2 patients. The cancer was therefore regarded as being free from T4 invasion and esophageal perforation in 59 of

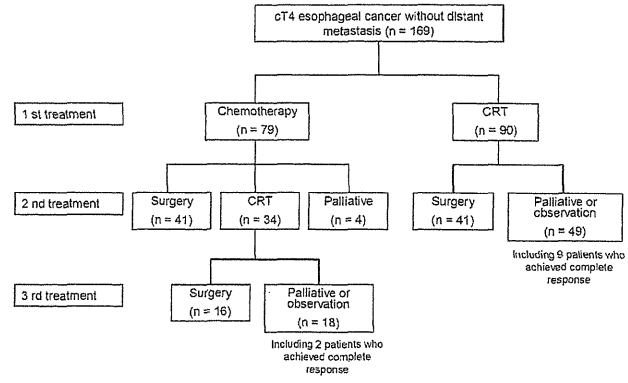

Fig. 1. Induction chemotherapy or chemoradiotherapy was conducted as initial treatment for 169 patients with T4 esophageal cancer free of distant metastasis. Subsequent therapy is also shown.

79 patients (74.9%) in the induction chemotherapy group and 52 of 90 patients (57.8%) in the chemoradiotherapy group.

Surgical resection was performed in 98 of 169 patients (58.0%). There was no significant difference in the rate of surgical resection between different tumor location, although the resection rate tends to be relatively high in lower third compared with upper or middle third (upper third; 55%, middle third; 57%, lower third; 67%). Surgical resection was performed in 57 of 79 patients (72.1%) in the induction chemotherapy group and 41 of 90 patients (45.6%) in the chemoradiotherapy group ($P = 0.0005$). Among 98 patients who underwent surgical resection, the rate of pathological CR tended to be higher in induction chemoradiotherapy group patients compared with those in the induction chemotherapy group, but this difference was not statistically significant (22% vs. 12%, $P = 0.2014$).

In patients who underwent surgical resection, there was no significant difference in rate of curative resection between induction chemotherapy group and chemoradiotherapy group. In 79 patients who underwent curative resection, there was no significant difference in the recurrence rate between induction chemotherapy group and chemoradiotherapy group. Moreover, the pattern of recurrence was almost similar between two groups (Table III).

Patient Survival

Across the 169 patients with T4 tumors, 3- and 5-year survival rates were 23.8% and 19.1%, respectively. The 98 patients who underwent surgical resection showed significantly better survival than those who did not undergo surgical resection (3- and 5-year survival; 48.2% and 39.8%, respectively vs. 7.0% and 3.5%, respectively; Fig. 2). This trend was continued in patients who showed a good response (CR/PR) to preoperative treatment (responder) and those who showed a poor response (SD/PD; non-responder) using separately analyzed survival data (Fig. 3A,B).

Next, we analyzed survival data according to the type of initial treatment. There was no significant difference in patient survival across the 169 study patients between the induction chemotherapy group and the chemoradiotherapy group, although the former group included more patients with distant lymph node metastasis compared with the chemoradiotherapy group (5-year survival rate: 23.1% vs. 16.9%, $P = 0.259$, Fig. 4). Univariate analysis of factors affecting survival across the two groups showed that response to preoperative treatment and surgical resection was significant associated with patient prognosis. However, there was no significant difference in the overall survival rate between different tumor location and different

TABLE II. Results of Preoperative Treatment for T4 Esophageal Cancers

	Total	Induction chemotherapy			
		Chemotherapy alone	Chemotherapy ± CRT[a]	Induction CRT[a]	*P* value
n	169	79	79	90	
Clinical response					
CR	19 (11)	0 (0)	3 (4)	16 (18)	0.0790[a]
PR	93 (55)	38 (48)	47 (59)	46 (51)	
SD/PD	57 (34)	41 (52)	29 (37)	28 (31)	
Esophageal perforation					
Yes	20 (12)	2 (3)	5 (6)	15 (17)	0.0379[a]
No	149 (88)	77 (97)	74 (94)	75 (83)	
Relief of T4 invasion without perforation					
Achieved	111 (66)	34 (43)	59 (75)	52 (58)	0.0209[a]
Not achieved	58 (34)	45 (57)	20 (25)	48 (42)	
Surgical resection					
Performed	98 (58)	41 (52)	57 (72)	41 (46)	0.0005[a]
Not performed	71 (42)	38 (48)[b]	22 (28)[b]	49 (54)[c]	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
CRT, chemoradiotherapy.
[a]Comparing induction chemotherapy ± CRT to induction CRT.
[b]Including 2 patients in whom surgical resection was not performed due to achievement of CR.
[c]Including 11 patients in whom surgical resection was not performed due to achievement of CR in 8 and 3 who refused the treatment.

T4 organs. Multivariate analysis also identified response to preoperative treatment and surgical resection as independent prognostic factors in patients with T4 esophageal cancers (Table IV).

DISCUSSION

It is not uncommon that esophageal cancer invades adjacent structures (T4), but there is no consensus on the standard treatment for such cases. Chemoradiotherapy is widely considered appropriate as the initial treatment for patients with T4 esophageal cancer, but induction chemotherapy is now a second potentially effective treatment option. The present study investigated whether induction chemotherapy using multiple anti-cancer drugs is a suitable initial treatment for patients with T4 esophageal cancers. We found that induction triplet chemotherapy using ACF or DCF reduced esophageal perforation and increased the resectability of T4 esophageal cancer by combining second-line chemoradiotherapy.

Many investigators believe that definitive chemoradiotherapy is appropriate for patients with unresectable esophageal tumors. Previous studies evaluating the efficacy of definitive chemoradiotherapy for patients with T4 and/or M1 lymph node esophageal cancers reported 3-year survival rates of 23–24% [13,16]. However, the survival rate was poor for patients who underwent chemoradiotherapy only for T4 esophageal cancers and not for non-T4 M1 lymph node cancers [9,11,13]. Ohtsu et al. [13] reported that survival rate in patients with T4 tumors was worse than in those with non-T4 M1 lymph tumors, with the 3-year survival rate of patients with T4 tumors being 14%. Itoh et al. [11] also showed that the 3-year survival rate of patients who underwent chemoradiotherapy for T4 tumors was only 10%. Our result showed better survival for patients with T4 tumors (3-year survival rate, 23.8%), by aggressively performing surgical resection when T4 tumor invasion was relieved. This result suggests that conducting surgical resection after

TABLE III. Results of Surgical Treatment for T4 Esophageal Cancers

	Total	Induction chemotherapy	Induction CRT	*P* value
n	169	57	41	
Pathological response				
Path CR (grade 3)	16 (16)	7 (12)	9 (22)	0.2014
Path non-CR (grade 0–2)	82 (84)	50 (88)	32 (78)	
Curative resection				
Non-curative	19 (79)	11 (19)	8 (20)	0.9789
Curative	79 (81)	46 (81)	33 (80)	
Recurrence				
Absent	38 (48)	23 (50)	15 (45)	0.6900
Present	41 (52)	23 (50)	18 (55)	
Lymphatic	28 (35)	16 (35)	11 (33)	0.8934
Distant	20 (25)	12 (26)	8 (24)	0.8525
Local	12 (15)	8 (17)	4 (12)	0.5198

CR, complete response; CRT, chemoradiotherapy.

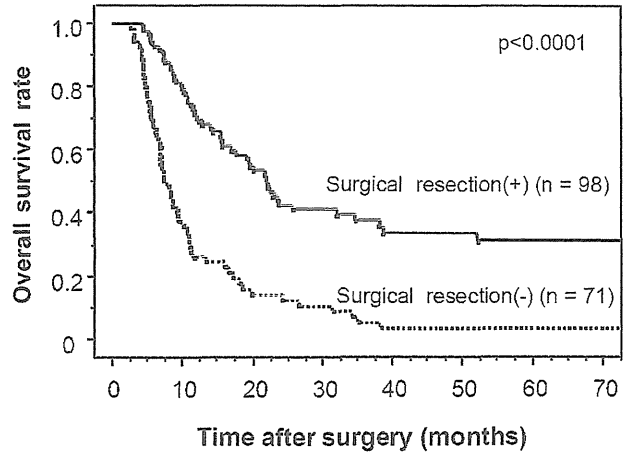

Fig. 2. Overall survival rate in 169 patients with T4 esophageal cancer without distant metastasis, according to surgical resection. The rates were significantly better in patients who underwent surgical resection than in those who did not undergo surgical resection.

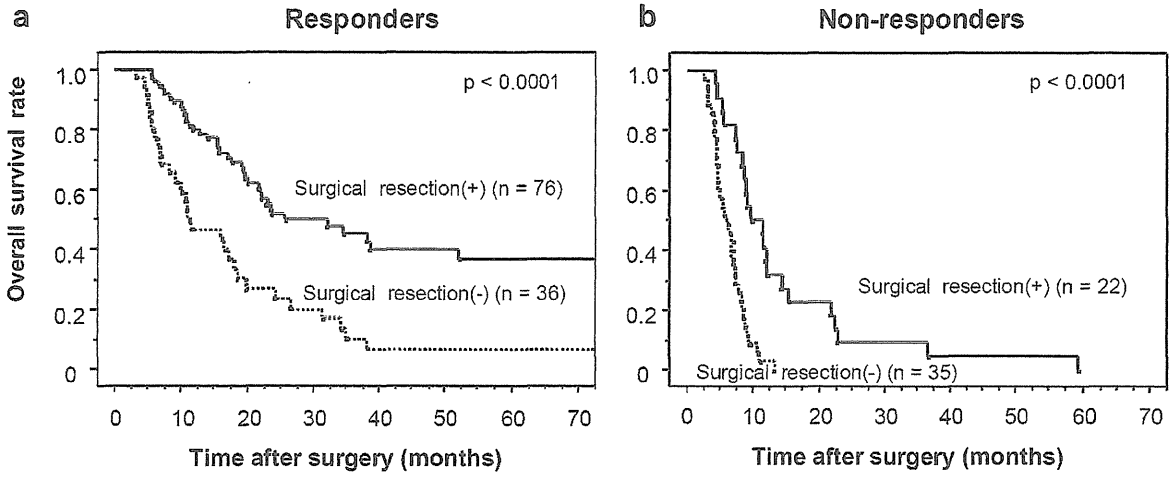

Fig. 3. Overall survival rate in 112 responders (A) and 57 non-responders (B), according to surgical resection. The overall survival rate was significantly better in patients who underwent surgical resection than in those who did not undergo surgical resection, irrespective of being a responder or non-responder.

preoperative treatment may improve prognosis in patients with T4 esophageal cancers.

In the present study, the rate of surgical resection was lower in patients undergoing induction chemoradiotherapy as initial treatment than in those undergoing induction chemotherapy, although there was no significant difference in the overall response rate between the two groups. One possible explanation for this statistic is that esophageal perforation occurred more frequently in patients who underwent induction chemoradiotherapy than in those who underwent induction chemotherapy (16.7% vs. 6.3%). Previous studies showed that such perforation during definitive chemoradiotherapy for patients with T4 esophageal cancer is not rare, with Ohtsu et al. [13] reporting a frequency of 14% (5 of 36 patients). Nishimura et al. [12] also showed that 18% of patients with T4 tumors developed new or worsened esophageal fistulae during chemoradiotherapy, while Roussel et al. [29] reported the development of esophageal fistulae in 29% of patients with esophagobronchial involvement who were treated with palliative radiotherapy alone. The current study showed a much lower rate of esophageal perforation in patients who were treated with induction chemotherapy compared to these previous studies, although that of patients who were treated with chemoradiotherapy in this study is almost equivalent to previous results. Moreover, 10 of 15 patients who experienced esophageal perforation in the chemoradiotherapy group in this study were responders. Thus, one reason for the lower resectability rate in the induction chemoradiotherapy group may be that responders sometimes experience esophageal perforation during chemoradiotherapy for T4 esophageal cancer.

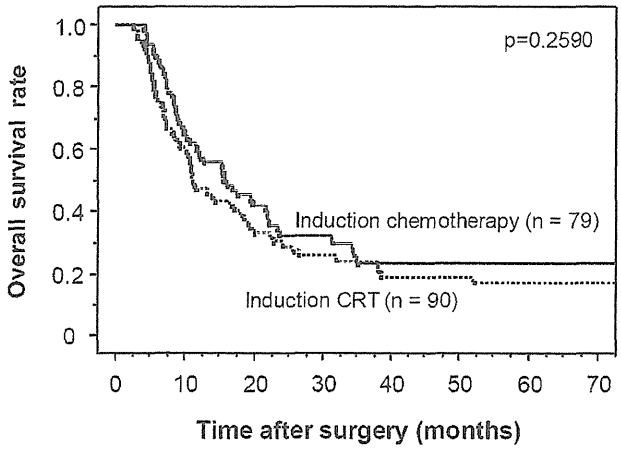

Fig. 4. Overall survival rate according to initial therapy in 169 patients with T4 tumors.

Another possible explanation for the lower resectability rates in patients undergoing induction chemoradiotherapy compared with those treated with induction chemotherapy is that it is more difficult to evaluate whether T4 invasion was relieved after chemoradiotherapy, compared with the cases after chemotherapy. In preoperative chemoradiotherapy, radiation-induced fibrotic or inflammatory changes may make it difficult to objectively assess the amount of residual tumor area by conventional radiological imaging [30,31]. Thus, histopathological assessment of tumor regression using resected specimens is commonly used to evaluate tumor response to preoperative chemoradiotherapy [32–35]. On the other hand, chemotherapy-induced fibrotic changes in the tumor and surrounding tissues were weak in the patient treated with preoperative chemotherapy [36], making clinical evaluation of residual tumors by radiological imaging a useful prognostic method. In fact, among 36 responders who did not undergo surgical resection in this study, seven in the chemoradiotherapy group were not regarded as achieving relief of T4 invasion compared to only 3 patients in the induction chemotherapy group. Thus, it is possible that chemoradiotherapy-induced fibrotic and inflammatory responses lead us to underestimate the resectability of T4 esophageal cancers.

In this study, patients who underwent surgical resection showed better survival compared with those not treated surgically, irrespective of their responder/non-responder status. This result is not coincident with previous studies, which demonstrated that patients with a good response to preoperative chemoradiotherapy achieved no survival benefit by subsequent surgical treatment [37,38]. This discordance may arise from the difference in patient characteristics in that the majority of patients enrolled in those previous studies had resectable non-T4 disease, unlike in our study. The previous studies