and human studies have demonstrated that rikkunshito promotes gastric adaptive relaxation [2, 9, 10], and accelerates gastric emptying [1, 5, 11, 12]. In addition, rikkunshito has been reported to have protective effects on the gastric mucosa [13] and to increase gastric surface mucin [14]. The effects of rikkunshito on gastrointestinal motor activity have yet to be evaluated.

Ghrelin is an endogenous ligand for the growth hormone secretagogue receptor, and it is known to have an intense appetite-enhancing effect [15]. Treatment with ghrelin enhances gastrointestinal motility [16] and increases food intake [17]. In addition, changes in plasma ghrelin levels have been reported in various gastrointestinal diseases, including FD [18–20]. A recent study demonstrated that rikkunshito suppresses cisplatin-induced decreases in plasma acylated ghrelin levels and increases food intake in rats, effects mediated by 5-HT2B/2C receptors [21]. Furthermore, rikkunshito increases plasma acylated ghrelin levels in healthy human volunteers and in normal mice [22]. These findings suggest that one mechanism by which rikkunshito acts is the enhancement of circulating ghrelin concentrations.

In the present study, we investigated the effects of rikkunshito on upper gastrointestinal motility and plasma ghrelin concentrations in conscious dogs.

Materials and methods

Animal preparation

Eleven healthy male and female beagle dogs, weighing between 10 and 12 kg, were divided into two groups: a normal group ($n = 6$) and a vagotomy group ($n = 5$). All procedures were approved by the Review Committee on Animal Use of Gunma University, Maebashi, Japan (No. 08-043).

The dogs were anesthetized with a single intravenous (IV) injection of thiopental sodium (Ravonal, Tanabe Pharmaceutical Co., Ltd., Osaka, Japan; 20 mg/kg body weight), and general anesthesia was maintained by intratracheal inhalation of halothane (Fluothane, Takeda Chemical Industries, Ltd., Osaka, Japan) and oxygen. A silastic tube (Silastic 602-205, Dow Corning, Midland, MI, USA) was inserted into the superior vena cava through a branch of the right external jugular vein and used as a central venous catheter (CVC) for the withdrawal of blood samples and for injections of drugs. The CVC was exteriorized through a skin incision on the neck, and fixed to the adjacent skin with silk sutures. A ventral midline incision was made to open the abdominal cavity.

In the normal group, force transducers [23] were implanted onto the serosal surfaces of the gastric body, gastric antrum, mid-duodenum and two sites on the jejunum (20 and 40 cm distal to Treitz's ligament, respectively) to detect circular muscle contractions. A silastic tube was inserted into the body of the stomach for drug administration (referred to as the gastric catheter).

In the vagotomy group, the ventral and dorsal vagi were cut immediately caudal to the diaphragm. Force transducers and a gastric catheter were then implanted similarly to the normal group.

The lead wires of the force transducers and the silastic tube were passed out of the abdominal cavity through a subcutaneous tunnel and brought out through a skin incision made between the right and left scapula. After closure of the abdominal cavity, a jacket-type protector was placed on each dog to protect the lead wires and tubes from damage by the dog. The dogs were housed in individual experimental cages, given intravenous drip infusions of Lactec G (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) for five postoperative days, and gradually returned to a diet of normal dog food (Funabashi Farm Inc., Funabashi, Japan; 15 g/kg body weight/day).

Monitoring of gastrointestinal contractions

The wires from the transducers were attached to a telemeter and the data were transmitted to a recording system (Eight Star System, Star Medical, Tokyo, Japan). The recorded signals were used to identify the phases of contractile activity. In addition, the data were used to determine the motility index (MI) references. The MI was the integrated area between the baseline level (level zero) and the contractile wave expressed as motor units.

Experimental procedures

Intragastric administration of rikkunshito in the normal group

A powdered extract of rikkunshito (Tsumura and Company, Tokyo, Japan), consisting of the following eight constituents, was used: *Glycyrrhizae radix* (4.7 %), *Zingiberis rhizoma* (2.3 %), *Atractylodis lanceae rhizoma* (18.6 %), *Zizyphi fructus* (9.3 %), *Aurantii nobilis pericarpium* (9.3 %), *Ginseng radix* (18.6 %), *Pinelliae tuber* (18.6 %), and *Hoelen* (18.6 %). Thirty milliliters of distilled water containing the powdered extract of rikkunshito (1.3, 2.7, and 4.0 g) was administered into the stomach through a gastric catheter 10–15 min after the end of interdigestive phase III contractions in the jejunum (distal transducer). 1.3 g of powdered extract of rikkunshito is equivalent to one commercially available packet of rikkunshito preparation. The gastrointestinal motor response to the intragastric administration of 30 ml of distilled water was used as a control.

Intravenous administration of antagonists combined with intragastric administration of rikkunshito in the normal group

To study the mechanism of rikkunshito-induced contractions, the muscarinic receptor antagonist atropine (0.1 mg/kg, Tanabe Pharmaceutical, Osaka, Japan), the nicotinic receptor antagonist hexamethonium (5 mg/kg, Wako Pure Chemicals), the 5-HT type 3 (5-HT3) receptor antagonist ondansetron (0.3 mg/kg, Chugai Pharmaceutical, Tokyo, Japan), or 30 ml of distilled water as a control was injected intravenously 10 min after the end of phase III contractions in the jejunum. The doses of atropine, hexamethonium, and ondansetron used in this study were previously reported to inhibit interdigestive phase III contractions in the stomachs of conscious dogs [24–26]. A powdered extract of rikkunshito (2.7 g) was administered intragastrically 5 min after the intravenous infusion of the antagonist.

Intragastric administration of rikkunshito in the vagotomy group

Thirty milliliters of distilled water containing powdered extract of rikkunshito (2.7 g) was administered into the stomach through the gastric catheter 10–15 min after the end of interdigestive phase III contractions in the jejunum.

Gastric emptying in the normal group

Each gastric emptying study was performed in the three - weeks after surgery. Gastric emptying was evaluated by the acetaminophen method. Acetaminophen absorption was used as an indirect measure of gastric emptying [27, 28]. After 12 h of fasting, powdered extract of rikkunshito (1.3, 2.7, and 4.0 g) or saline was administered into the stomach through the gastric catheter to five dogs. Thirty minutes later, the dogs were fed 300 g of dog food (Cainz Dog Meal, Cainz, Takasaki, Japan) including 500 mg of acetaminophen (Calonal, Showa Yakuhin Kako, Tokyo, Japan). Blood samples were withdrawn from the jugular catheters 0, 15, 30, 45, 60, 75, 90, 105, 120, 135, and 150 min after feeding. The serum acetaminophen concentrations were determined with an automatic fluorescence polarization immunoassay (TDx, Abbott Laboratories, North Chicago, IL, USA) by the Department of Pharmacy, Gunma University Hospital.

Measurement of plasma acylated ghrelin concentrations in the normal group

Five dogs were administered rikkunshito at four doses (0, 1.3, 2.7, and 4.0 g) on four different days in random order. Tests were performed at 0900 hours after overnight fasting. Basal blood samples were obtained at 0 min (baseline), and rikkunshito was then administered. Additional blood samples were obtained at 30, 60, 90, 120, 150, 180, 240, and 300 min. The blood samples were transferred into chilled tubes containing ethylenediaminetetraacetic acid-2Na and 500 U aprotinin, and promptly centrifuged at 4 °C and $3000 \times g$. The supernatants were then acidified with 1 mol/l HCl (1/10 volume). All plasma samples were stored at − 80 °C until hormone analyses were performed. Plasma acylated ghrelin concentrations were determined using an Active Ghrelin Enzyme-Linked Immunoassay Kit (Mitsubishi Kagaku Iatron Inc., Tokyo, Japan). This kit employs a polyclonal antibody against N-terminal fragments containing *n*-octanoylated serine at position 3. These assay kits were designed for rats, mice, and humans, but a recent study used them to accurately measure ghrelin in dogs [29]. The values were normalized as percentages of the baseline value.

Statistical analysis

All results are expressed as mean ± SEM. Time-dependent changes in plasma hormone levels were compared by two-way analyses of variance with repeated measurements on two factors and univariate testing of significance for planned comparisons. The paired data were compared using Student's *t* test. *P* values of <0.05 were considered to indicate statistical significance. Statistical analyses were carried out using JMP 5.01 software (SAS Institute Inc., Cary, NC, USA).

Results

Effect of rikkunshito on upper gastrointestinal motility in fasted dogs

In fasted dogs, cyclic gastric contractions were detected, including a quiescent period followed by a group of strong contractions (phase III). Intragastric administration of 30 ml of distilled water as a control did not induce any apparent motor effect at any site. Intragastric administration of powdered extract of rikkunshito at doses of 1.3, 2.7 and 4.0 g induced phasic contractions mainly in the duodenum and jejunum (Fig. 1). The MI of rikkunshito-induced contractions in the gastric antrum, duodenum, and jejunum increased in a stepwise fashion up to a dose of 2.7 g; a higher dose of 4.0 g of rikkunshito did not augment this effect (Fig. 2). After the completion of rikkunshito-induced contractions, spontaneous interdigestive migrating contractions (IMC) occurred. Rikkunshito-induced contractions did not affect the time lag between the administration of rikkunshito and the initiation of the

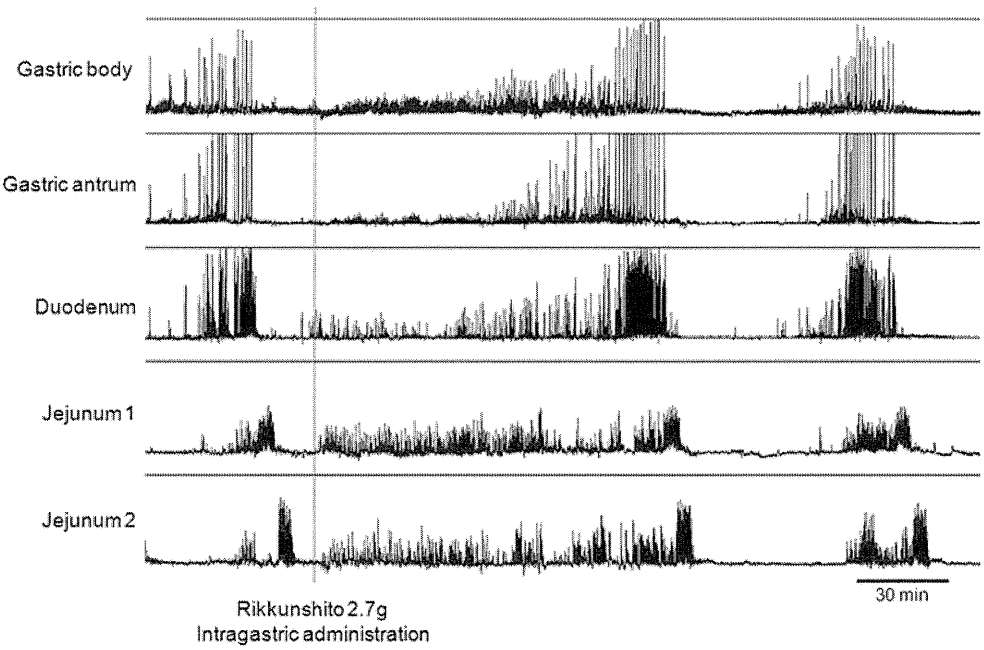

Fig. 1 Effects of intragastric administration of rikkunshito on gastrointestinal motility during the interdigestive state in the normal group. Rikkunshito induced phasic contractions lasting for about 30 min in the duodenum and jejunum

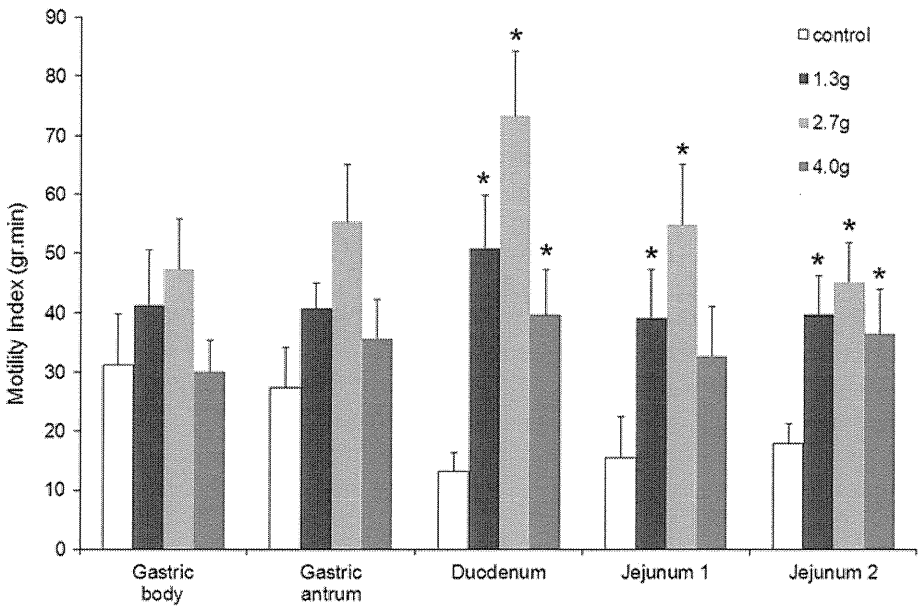

Fig. 2 The MI for 30 min after intragastric administration of rikkunshito. The MI of rikkunshito-induced contractions in the duodenum and jejunum increased in a stepwise fashion up to a dose of 2.7 g. A higher dose of 4.0 g of rikkunshito did not augment this effect

next phase III IMC in the gastric body as compared with the control (control: 109.8 ± 10.1 min; 1.3 g: 125.8 ± 7.0 min; 2.7 g: 130.4 ± 14.6 min; 4.0 g: 133.8 ± 20.2 min).

Effects of rikkunshito on upper gastrointestinal motility in fed dogs

After food intake, the fasted motor pattern was immediately disrupted and replaced by the fed motor pattern, which consisted of irregular, high-frequency contractions. When rikkunshito (1.3, 2.7, 4.0 g) was intragastrically administered to dogs 30 min after feeding, the fed motor pattern persisted (Fig. 3), and the MI did not significantly differ from the pattern after intragastric administration of saline (data not shown).

Effect of antagonists on intragastric rikkunshito-induced contractions

Atropine and hexamethonium abolished rikkunshito-induced contractions. Ondansetron inhibited rikkunshito-induced contractions, slightly but not significantly (Fig. 4).

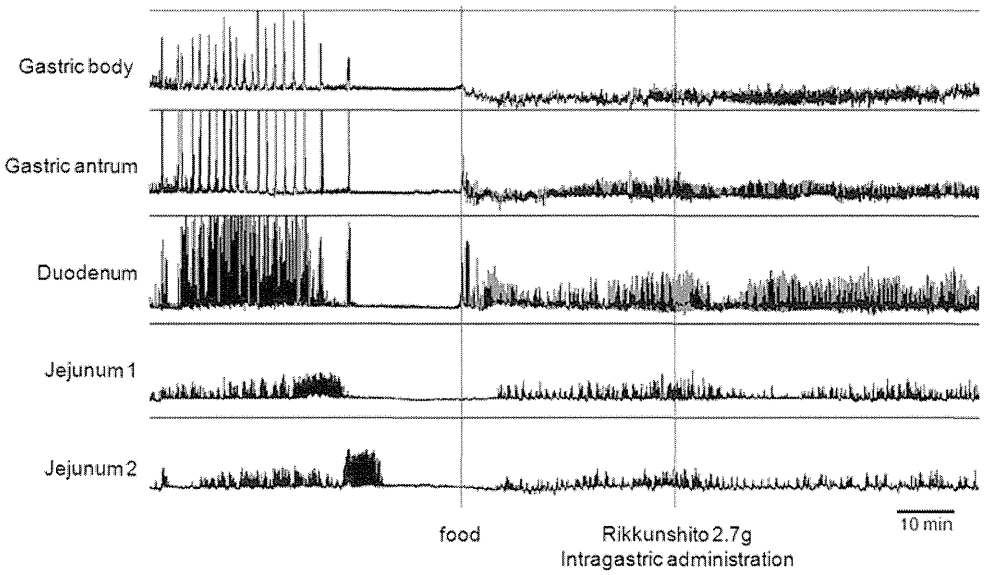

Fig. 3 Effects of rikkunshito on upper gastrointestinal motility in the fed state. After food intake, the fasting motor pattern was immediately disrupted and replaced by the fed motor pattern, characterized by irregular, high-frequency contractions. Rikkunshito had no significant effect on the fasted motor pattern

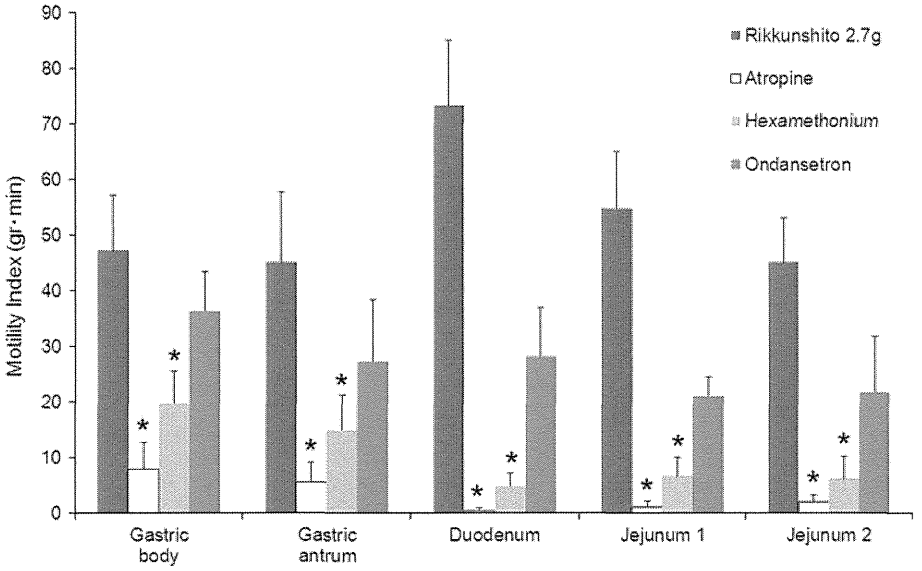

Fig. 4 Effects of antagonists on the MI for 30 min during the motor response induced by intragastric administration of 2.7 g rikkunshito. Atropine and hexamethonium significantly inhibited the upper gut MI of rikkunshito-induced contractions at all sites

Intragastric administration of rikkunshito in the truncal vagotomy group

After truncal vagotomy, phase III contractions of the stomach were observed in an immature form. Intragastric administration of powdered extract of rikkunshito (2.7 g) induced phasic contractions in the duodenum and jejunum, as was observed in the normal group (Fig. 5).

Effects of rikkunshito on gastric emptying

Intragastric administration of rikkunshito accelerated gastric emptying in a dose-dependent manner. 2.7 and 4.0 g of powdered extract of rikkunshito significantly accelerated gastric emptying as compared with the control ($p < 0.05$ at 105, 120, 135, 150 min in dogs given 2.7 g; $p < 0.05$ at 90, 105, 120, 135, 150 min in dogs given 4.0 g; Fig. 6).

Effect of rikkunshito on plasma acylated ghrelin concentrations

Although tests were performed under the same conditions, a large variability in actual baseline acylated ghrelin levels (44.9–277.6 pg/ml) was found among dogs. Therefore, the ratios of each time value to baseline acylated ghrelin concentrations were calculated. After administration of 4.0 g of rikkunshito, the levels of plasma acylated ghrelin gradually increased as compared with the baseline value, and the increased ratio 150 min after administration was much higher than that in the control group (control: 106.6 ± 7.4 %; 4.0 g: 157.1 ± 18.6 %; Fig. 7).

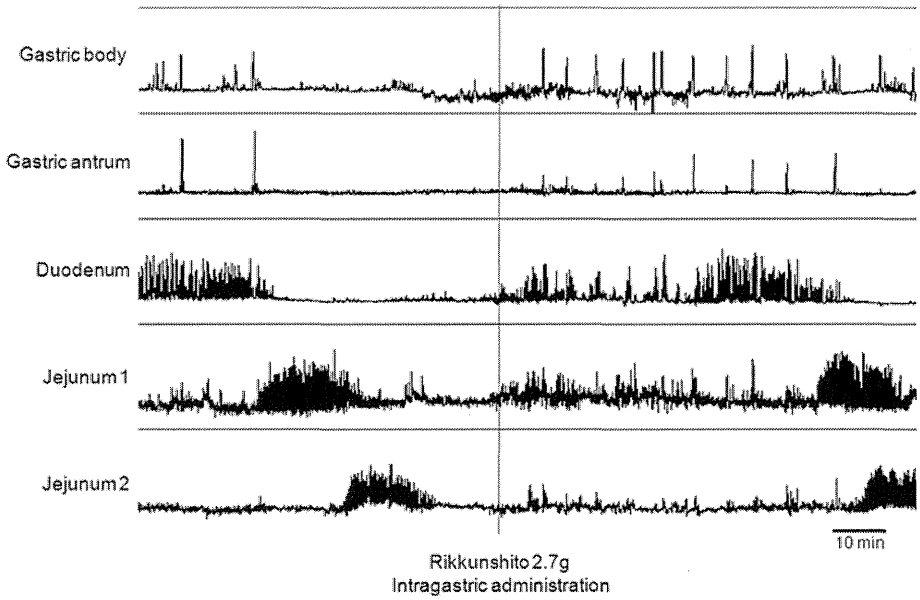

Fig. 5 Effects of intragastric administration of rikkunshito on gastrointestinal motility during the interdigestive state in the truncal vagotomy group. Intragastric administration of rikkunshito induced phasic contractions in the duodenum and jejunum, as observed in the normal group

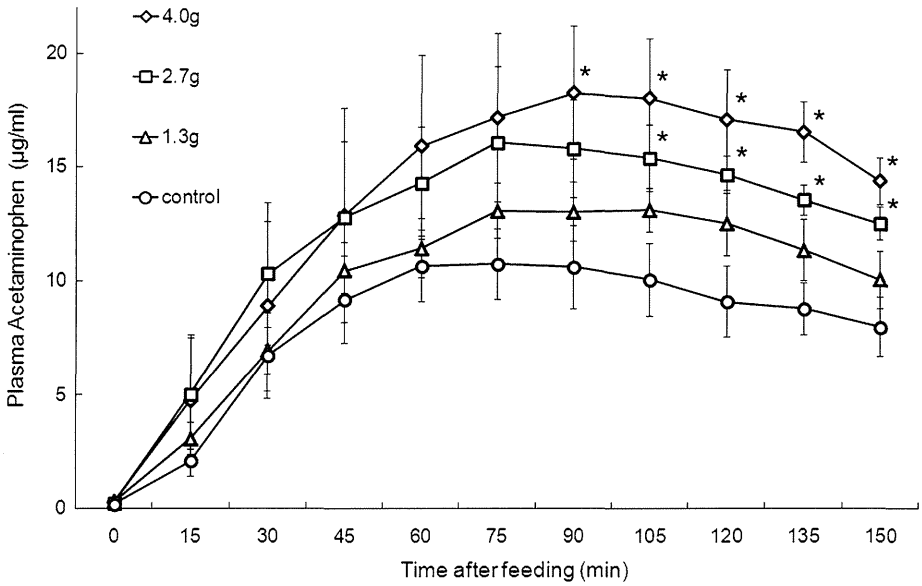

Fig. 6 Effects of intragastric administration of rikkunshito on gastric emptying. Rikkunshito accelerated gastric emptying in a dose-dependent manner and 2.7 and 4.0 g of rikkunshito significantly accelerated gastric emptying as compared with the control

Discussion

In fasted dogs, intragastric administration of rikkunshito evoked phasic contractions mainly in the duodenum and jejunum. Rikkunshito-induced contractions did not affect the contractile pattern of the next IMC. The MI of intragastric rikkunshito-induced contractions increased gradually in a dose-dependent fashion, but the response to 4.0 g was not greater than that of 2.7 g. Rikkunshito consists of the eight constituent medical herbs described above and contains many compounds. Effective dosages and administration procedures for traditional Japanese medicine are based on extensive clinical experience with herbal combinations accumulated over thousands of years. Rikkunshito has been shown to promote relaxation of the proximal stomach in humans, as confirmed by barostat studies and ultrasonography [2, 9, 10, 30, 31]. Rikkunshito may have opposing dual actions on gastrointestinal motility. Such dual effects may result in balancing out opposing actions, causing dose-related differences in contractile response.

We investigated the effects of several antagonists on contractions induced by rikkunshito. Intragastric rikkunshito-induced contractile activity was abolished by atropine and hexamethonium and inhibited by ondansetron. 5-HT3 receptor antagonists have been reported to inhibit subsequent phase III activity completely in the stomach and partially in the duodenum [32]. These findings indicate that the contractile effect of rikkunshito is mediated by cholinergic neurons and that 5-HT3 receptors have a partial role in this action.

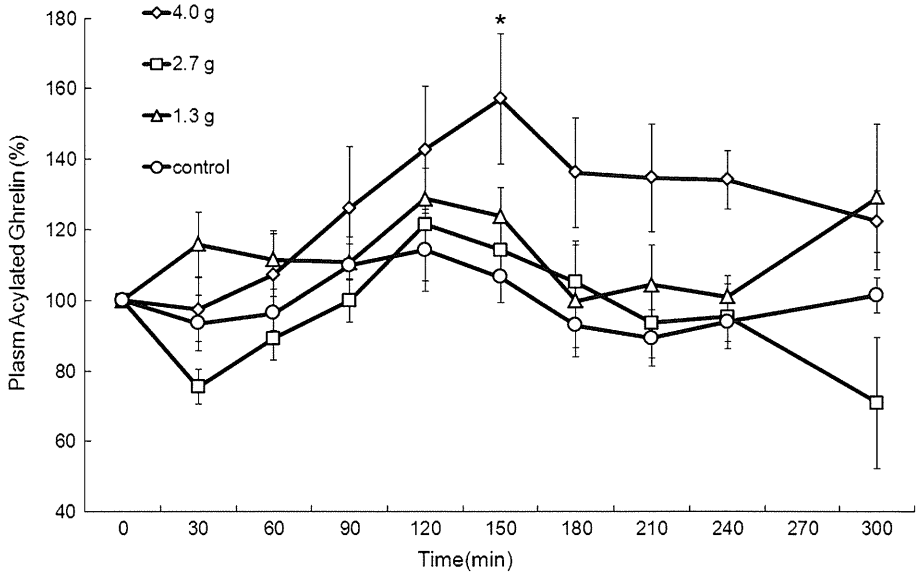

Fig. 7 Effect of rikkunshito on plasma acylated ghrelin concentrations. After administration of 4.0 g of rikkunshito, plasma acylated ghrelin levels gradually increased, and the increase 150 min after administration was highly significant as compared with that in the control group

The effect of rikkunshito on gastrointestinal motility appeared promptly after drug administration. The mechanism of the contractile effects of rikkunshito most likely involves a direct action on the gastrointestinal mucosa rather than increased plasma concentrations of active ingredients. Rikkunshito also induced contractions in the truncal vagotomy group. This finding suggests that rikkunshito directly stimulates the local enteric nervous system.

Daikenchuto is the most frequently prescribed traditional Japanese medicine in Japan. Daikenchuto consists of three different herbs: 50 % dried ginger rhizome, 30 % ginseng root, and 20 % zanthoxylum fruit. Daikenchuto has been used to treat abdominal obstructions, including bowel obstruction, and a feeling of abdominal coldness. Similar to rikkunshito, daikenchuto stimulates gastrointestinal motility through cholinergic and 5-HT3 receptors, and its contractile effects are attributed to a direct action on the gastrointestinal mucosa [33, 34]. In contrast to rikkunshito, daikenchuto induces contractions in the gastric antrum, duodenum, and jejunum, and the duration of contractile responses induced by daikenchuto is shorter than that induced by rikkunshito. These differences might be attributed to the different components of these two medicines.

In the present study, rikkunshito accelerated gastric emptying in a dose-dependent manner up to a dose of 2.7 g. A higher dose of 4.0 g did not augment this effect. Pharmacologically, therefore, the acceleration of gastric emptying by rikkunshito may not involve rikkunshito-induced contractions. In addition, rikkunshito did not stimulate postprandial contractions. Previous studies reported that rikkunshito accelerates gastric emptying [1, 11, 12]. Initially, the actions of rikkunshito were ascribed to the promotion of nitric oxide (NO)-associated gastric adaptive relaxation because it contains L-arginine, a substrate for NO production. However, Tominaga et al. [12] showed that rikkunshito improved the 5-HT-induced delay in gastric emptying in rats, apparently by antagonizing the 5-HT3 receptor pathway. In the present study, we did not study the mechanism by which rikkunshito stimulates gastric emptying. Gastric empting is regulated by various factors, such as gastric accommodation, antral contraction, pyloric opening and closing, duodenal motility, and gastroduodenal coordination. We believe that the role of rikkunshito in promoting gastric motility may also involve other factors. Further investigations are needed to clarify the mechanisms by which rikkunshito promotes gastric emptying.

In the present study, gastric emptying was evaluated by the acetaminophen method using semisolid foods. Plasma concentrations of acetaminophen may reflect gastric emptying of liquids, but gastric empting of solid food may differ. This point is a limitation of the present study.

Rikkunshito has been reported to be effective against many gastrointestinal symptoms but its mechanism of action has not been fully elucidated. In the present study, we showed that rikkunshito increases contractile activity in the proximal small intestine and accelerates gastric emptying. Although further investigations are needed, we speculate that these prokinetic effects have a role in the mechanism by which rikkunshito ameliorates gastrointestinal symptoms.

Traditional Japanese medicine has been systematized on the basis of thousands of years of clinical experience with herbal combinations. Most traditional Japanese medicines consist of a number of crude drugs. Rikkunshito is extracted from a mixture of *Atractylodis lanceae rhizoma*,

Ginseng radix, *Pinelliae tuber*, Hoelen, *Zizyphi fructus*, *Aurantii nobilis pericarpium*, *Glycyrrhizae radix*, and *Zingiberis rhizoma*. *Ginseng radix* and *Pinelliae tuber* are associated with gastric emptying [1], *Zingiberis rhizoma* [35] and *Atractylodis lanceae rhizoma* [36] are reported to improve the delayed gastric emptying induced by NG-nitro-L-arginine. Hesperidin and heptamethoxyflavone, components of *Aurantii nobilis pericarpium*, improve upper gut motility [11]. However, the concentrations of these ingredients in rikkunshito are lower than the doses used in previous studies. The active crude ingredients of rikkunshito are thought to act synergistically to produce therapeutic effects. Therefore, clarification of the pharmacologic effects of individual agents may not lead to an overall understanding of traditional Japanese medicines.

In the present study, administration of 4.0 g of powdered extract of rikkunshito significantly increased plasma acylated ghrelin levels 150 min after administration. In our preliminary experiments, we measured plasma acylated ghrelin concentrations sequentially in the fasted state. In the present experiment, rikkunshito increased acylated ghrelin concentrations to nearly the peak level in the fasted state. Ghrelin is known to have an intense appetite-enhancing effect [17], and also stimulates gastric motility and gastric acid secretion in rats [16, 37, 38]. However, Ohno et al. [39] reported that ghrelin did not stimulate gastrointestinal motility in dogs. Takeda et al. [40] reported that rikkunshito suppressed cisplatin-induced decreases in plasma acylated ghrelin levels in rats, an effect that was apparently mediated by 5-HT2B and 5-HT2C receptors. Matsumura et al. [22] demonstrated that rikkunshito increased plasma acylated ghrelin levels in healthy human volunteers and in normal mice after two weeks of treatment. Recently, Takeda et al. [41] reported that regulation of ghrelin secretion under normal conditions is unaffected by 5-HT2B or 5-HT2C activation and that rikkunshito increases circulating acylated ghrelin levels by inhibiting deacylation under normal conditions. These reports are consistent with our results. We did not study the mechanism by which rikkunshito increases plasma ghrelin levels. However, because time lag between rikkunshito administration and increase of plasma ghrelin levels was long, we do not believe it was due to a direct effect on the gastric mucosa. The mechanism regulating ghrelin secretion remains unknown. We speculate that rikkunshito may increase plasma ghrelin levels, at least in part, by inhibiting the ghrelin degradation [21], and by increasing secretion of ghrelin by an unknown mechanism. Rikkunshito might be a useful treatment for anorexia and may provide a new strategy for improvement of upper gastrointestinal symptoms.

In conclusion, intragastric administration of rikkunshito stimulated gastrointestinal contractions in the interdigestive state and accelerated gastric emptying. Moreover, rikkunshito increased plasma acylated ghrelin levels. Rikkunshito may alleviate gastrointestinal tract disorders through its prokinetic effects.

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Conflict of interest The authors have no conflicts of interest to declare.

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cer. Over the past decade, the results of clinical studies in patients with metastatic colorectal cancer have revealed substantial improvements in survival [1, 2]. 5-Fluorouracil (5-FU)-based chemotherapy is the mainstay of treatment for patients with metastatic colorectal cancer. Combinations of infusional 5-FU, leucovorin and oxaliplatin (FOLFOX) and infusional 5-FU, leucovorin and irinotecan (FOLFIRI), with or without molecular targeting agents, are considered standard treatments for metastatic colorectal cancer [1–5]. The order of combinations for first- and second-line treatment, for example FOLFOX followed by FOLFIRI or FOLFIRI followed by FOLFOX, does not affect patient survival [1]. However, 20–30% of patients do not proceed to second-line treatment [6]. Therefore, adequate and active first-line treatment is essential in the treatment of colorectal cancer. As exposure to active agents, i.e. 5-FU, oxaliplatin and irinotecan, rather than second-line therapy itself appears to predict improved survival [7], the 'up-front' administration of these 3 effective drugs may be the most effective means of improving outcomes. Consequently, several groups have investigated the triple-drug FOLFOXIRI regimen (5-FU, oxaliplatin and irinotecan) in patients with metastatic colorectal cancer to improve their prognosis [8, 9]. FOLFOXIRI resulted in significant increases in activity, efficacy and improvements in the long-term outcome. However, the triple-drug regimen causes further adverse effects [10, 11]. In particular, neurotoxicity is a common and frequent adverse event that diminishes the dose that can be administered [8, 12]. We hypothesized that alternating oxaliplatin and irinotecan would allow patients to benefit from concurrent treatment with all 3 drugs as soon as they were diagnosed with metastatic disease while allowing them to recover from the adverse events associated with each drug before its administration was repeated. The aim of this study was to explore the efficacy and safety of alternating regimens of 4 cycles of mFOLFOX6 and 4 cycles of FOLFIRI (FIREFOX) in the first-line treatment of advanced colorectal cancer. Specifically, we wanted to evaluate the impact of this schedule on the dose-limiting neurotoxicity and diarrhea associated with oxaliplatin and irinotecan.

Methods

Eligibility Criteria

Patients with histologically proven, unresectable, advanced or metastatic colorectal cancer who had not received any previous treatment were eligible for the study if they met all of the following criteria: measurable disease, age ≥20 and ≤75 years, Eastern Cooperative Oncology Group performance status ≤2, life expectancy ≥3 months and adequate bone marrow, hepatic and renal function. Written informed consent was obtained from all patients prior to enrollment in the study. The ethical, medical and scientific aspects of the study were reviewed and approved by the ethics committees of each participating institution in the University Hospital Medical Information Network clinical trials registry (UMIN000001340). The study was conducted in accordance with the Declaration of Helsinki of 1975, revised in 2000.

Treatment Schedule

Patients received an alternating regimen of 4 cycles of mFOLFOX-6 (85 mg/m^2 oxaliplatin, 200 mg/m^2 leucovorin on day 1 followed by 400 mg/m^2 bolus 5-FU and a 46-hour 2,400-mg/m^2 5-FU infusion every 2 weeks) followed by 4 cycles of FOLFIRI (oxaliplatin replaced with 150 mg/m^2 irinotecan on day 1). This schedule was repeated until unacceptable toxicity or progressive disease (PD) was observed. Treatment was administered until the observation of PD or unacceptable toxicity, withdrawal of consent, the physician's decision to terminate, or interruption of treatment for >14 days occurred. Dose modification was performed based on the hematological parameters and the degree of non-hematological toxicities. Chemotherapy was delayed until recovery if neutrophil counts decreased to <1,500/mm^3, platelet counts decreased to <75,000/mm^3, or significant persistent non-hematological toxicity occurred. The 5-FU dose was reduced to 300 (bolus) or 500 mg/m^2 (infusion) if grade 3/4 diarrhea, stomatitis, nausea/vomiting, anorexia, dermatitis, grade 4 neutropenia, or grade 3/4 thrombocytopenia occurred. Oxaliplatin was also reduced to 65 mg/m^2 for the same conditions, except for the occurrence of dermatitis; additionally, it was reduced in cases of persistent (15 days or longer) grade 2 neurotoxicity or temporary (8–14 days) grade 3 neurotoxicity. In cases of persistent (15 days or longer) grade 3 neurotoxicity or temporary grade 4 neurotoxicity, oxaliplatin was omitted from the regimen. The irinotecan dose was reduced to 130 mg/m^2 for the same reasons as described for oxaliplatin. The use of Ca/Mg treatment was not regulated as part of this protocol.

Endpoints

The primary endpoint of the study was the response rate (RR), and the secondary endpoints were progression-free survival (PFS), overall survival (OS) and adverse effects. During the 4 weeks before chemotherapy was initiated, all patients underwent the following: physical examination, complete blood cell count, hepatic and renal function tests, and chest and abdominal computed tomography or magnetic resonance imaging. A physical examination, hepatorenal function tests and blood counts were performed before each cycle. Patients were assessed before starting each 2-week cycle according to the National Cancer Institute Common Toxicity Criteria version 3 [13]. Tumor evaluation was performed every month for the first 3 months and then every 2 months thereafter using the Response Evaluation Criteria in Solid Tumors version 1.0 [14]. A complete response (CR) was defined as the disappearance of all known lesions and the absence of new lesions. A partial response (PR) was defined as a reduction of 30% or more in the sum of the maximum tumor lengths of up to 10 known lesions and the absence of new lesions. Stable disease (SD) was defined as a reduction of <30% or an increase of <20% in the sum of the maximum tumor lengths of up to 10 known lesions and the absence of new lesions.

PD was defined as an increase of ≥20% in the sum of the maximum tumor lengths of up to 10 known lesions or as the appearance of at least 1 new lesion.

Statistical Considerations

Using the binomial exact method (DSTPLAN) with a null RR of 40%, an expected RR of 60%, one-sided $\alpha = 0.05$ and power of 80%, 42 patients were needed for the study. Allowing that 10% of patients would be ineligible or drop out, the planned target number of patients was 47. The confidence interval (CI) for the RR was estimated by the exact method. The duration of survival was measured from the day of entry into the study, and the OS and PFS curves were calculated by the Kaplan-Meier method. A one-sided $p < 0.05$ was considered statistically significant at the statistical test of the primary endpoint. All statistical analyses were performed using Stata version 11 statistical analysis software (Stata, College Station, Tex., USA).

Results

Patient Characteristics

Between July 2007 and June 2008, 48 patients in 25 institutions in Japan were enrolled in this trial. Two of the patients did not meet the eligibility criteria: 1 did not undergo a prior imaging examination and the other had multiple active cancers. Forty-seven patients were treated with protocol therapy. Response, OS and PFS were assessed in 46 patients. The characteristics of 47 patients and those eligible for study inclusion are listed in table 1. The median number of administration cycles was 12 (range 1–47). Toxicity and tolerability were assessed with all 47 patients who received protocol therapy.

Efficacy

The overall RR as determined by the independent committee was 58.7% (95% CI 43.5–73.5), and it included 1 CR (2.1%) and 26 PRs (56.5%). The number of instances of SD and PD were 14 (30.4%) and 2 (4.3%), respectively; 3 (6.5%) patients were not evaluable (table 2). The tumor control rate (CR + PR + SD) was 89.1%. Irrespective of the order of treatment, the period from registration to the first evidence of progression on imaging analysis was defined as PFS. After a median follow-up of 27.5 months, the median PFS was 10.3 months in the 46 assessable patients (95% CI 7.5–11.9; fig. 1), and the median OS was 28.4 months in those patients (95% CI 22.5–35.7; fig. 2). The 1-, 2- and 3-year survival rates were 84.5% (95% CI 70.5–92.4), 60.2% (95% CI 44.4–72.7) and 32.9% (95% CI 17.8–48.8), respectively. Surgery was performed in 9 patients (19.6%) after treatment.

Table 1. Baseline patient characteristics

Characteristic	All cases (n = 47)
Age, years	
Median	66
Range	43–75
Gender	
Male	35 (74.5)
Female	12 (25.5)
Performance status	
0	38 (80.9)
1	9 (19.1)
Existence of a primary tumor	
Yes	19 (40.4)
No	28 (59.6)
Site of the primary tumor	
C	1 (5.3)
A	3 (15.8)
T	3 (15.8)
D	1 (5.3)
S	5 (26.3)
RS	1 (5.3)
Ra	2 (10.5)
Rb	3 (15.8)

Figures in parentheses are percentages. C = Cecum; A = ascending colon; T = transverse colon; D = descending colon; S = sigmoid colon; RS = rectosigmoid colon; Ra = rectum above the peritoneal reflection; Rb = rectum below the peritoneal reflection.

Table 2. Antitumor efficacy

Response	Full analysis set (n = 46)
CR	1 (2.2)
PR	26 (56.5)
SD	14 (30.4)
PD	2 (4.3)
NE	3 (6.5)
Overall response rate (CR + PR)	27 (58.7)
95% CI	43.9–73.5*

Figures in parentheses are percentages. NE = Not evaluable.
* One-sided $p = 0.0008$ (exact method with the null RR = 40%).

Toxicity and Tolerability

The 4 cycles of FOLFOX6 and the 4 cycles of FOLFIRI could each be prescribed alternatively, although there were some treatment delays because of adverse reactions. In the shortest case, only 1 cycle was completed because

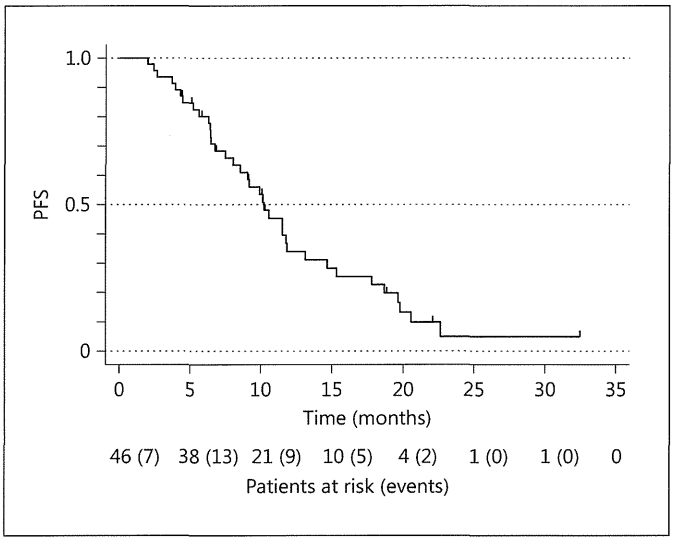

Fig. 1. Progression-free survival.

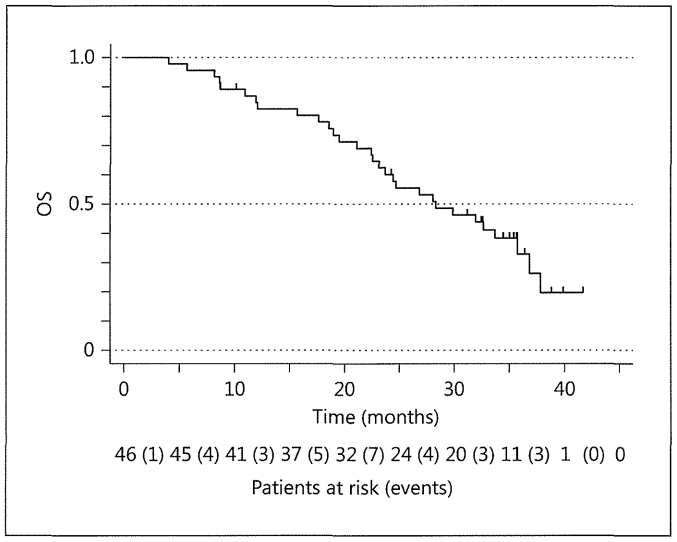

Fig. 2. Overall survival.

Table 3. Treatment-related adverse events

	All grades	G3	G4
Anorexia	32 (68.10)	4 (8.50)	0
Fatigue	27 (57.40)	2 (4.30)	0
Nausea	27 (57.40)	1 (2.10)	1 (2.10)
Mucositis	19 (40.40)	0	0
Constipation	17 (36.20)	0	0
Neurotoxicity (CTCAE)	17 (36.20)	0	0
Diarrhea	15 (31.90)	1 (2.10)	0
Alopecia	13 (27.70)	0	0
Vomiting	13 (27.70)	0	1 (2.10)
Fever	8 (17.00)	0	1 (2.10)
Hand-foot syndrome	6 (12.80)	0	0
Allergic reaction	4 (8.50)	0	0
Chromatosis	2 (4.30)	0	0
Febrile neutropenia	2 (4.30)	2 (4.30)	0
Insomnia	2 (4.30)	0	0
Pneumonia	2 (4.30)	1	0
Weight loss	2 (4.30)	0	0
Epistaxis	1 (2.10)	0	0
Gastrointestinal bleeding	1 (2.10)	0	0
Anemia	42 (89.40)	2 (4.30)	0
Neutropenia	41 (87.20)	17 (36.20)	9 (19.10)
AST elevated	39 (83.00)	3 (6.40)	0
Thrombocytopenia	35 (74.50)	2 (4.30)	0
ALT elevated	24 (51.10)	1 (2.10)	1 (2.10)
Total bilirubin elevated	9 (19.10)	0	0

Figures in parentheses are percentages.

of allergic reactions, whereas 47 cycles were completed in the longest case. The adverse events are shown in table 3. Among the 47 patients evaluated for toxicity, the most common grade 3–4 adverse events were leukopenia (26%), neutropenia (55%), anemia (4%), diarrhea (2%), febrile neutropenia (4%), nausea (4%), and vomiting (2%). No grade 3–4 neurotoxicity, which is a dose-limiting toxicity of oxaliplatin, was reported; only 1 case of grade 3–4 diarrhea was reported. Grade 3–4 hypersensitivity reactions were not reported. Figure 3 illustrates the occurrence of neurotoxicity for each patient in each cycle. Neurotoxicity occurred primarily during the FOLFOX cycles, although some of the neurotoxicity subsided during the FOLFIRI cycles.

Discussion

Among patients with unresectable colorectal cancers, the duration of survival has increased in the past decade. This improvement resulted primarily from the introduction of oxaliplatin or irinotecan into 5-FU-based regimens; additionally, molecular targeting agents have played a role in extending patient survival [1–5]. It is known that patient outcome is significantly improved with exposure to all active drugs in the course of disease treatment [1, 2]. Thus, the sequential administration of FOLFOX and FOLFIRI in any order with molecular targeting agents is the standard treatment for unresectable colorectal cancer [4, 5]. However, approximately 20–30%

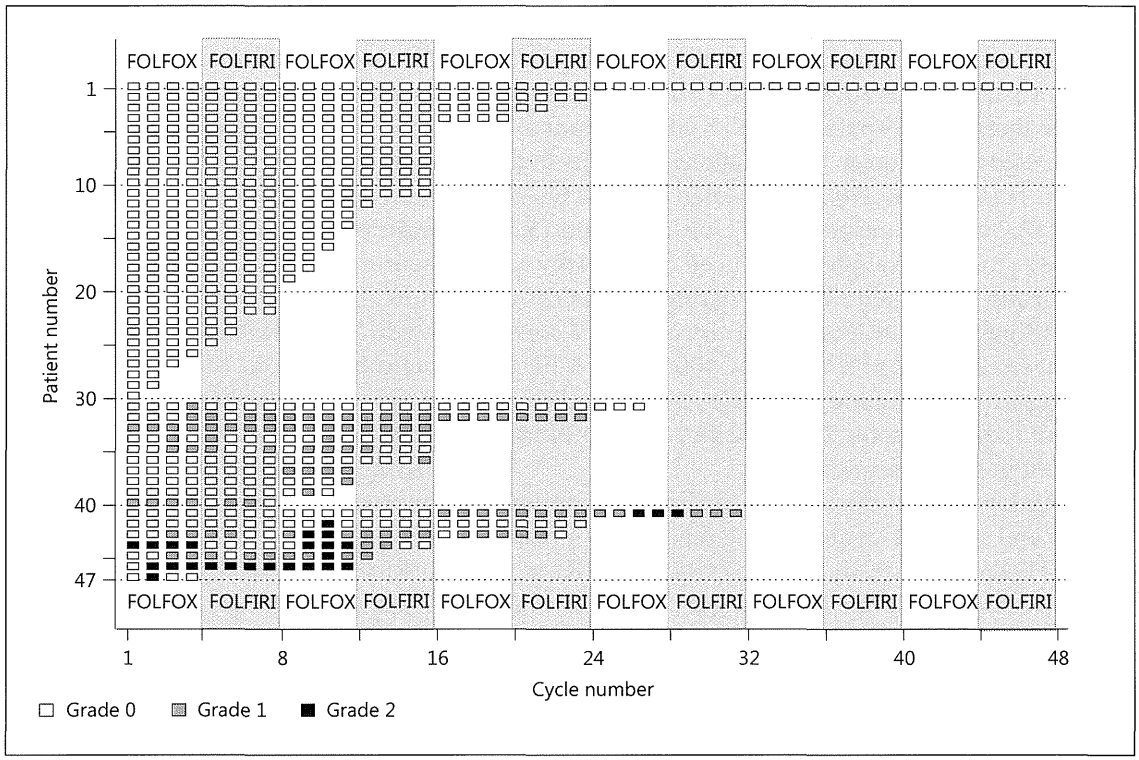

Fig. 3. Occurrence of neurotoxicity (CTCAE) in each cycle for all 47 patients. White squares indicate no toxicity; gray squares indicate grade 1 neurotoxicity; black squares indicate grade 2 neurotoxicity.

of patients exhibit PD after first-line therapy; hence, they do not receive further chemotherapy [6, 7]. Furthermore, an important limitation of this strategy is frequent grade 3 sensory neuropathy, which occurred in approximately one third of the patients initially treated using FOLFOX [15, 16]. This neuropathy forced many patients to stop oxaliplatin-containing treatment before tumor progression [1].

Three strategies have been proposed to avoid these toxicities and increase the rate of exposure to all active drugs. First, all 3 key drugs are administered during first-line therapy, as with the FOLFOXIRI regimen [8, 9, 12]. It is reported that combinations including irinotecan and oxaliplatin with 5-FU (FOLFOXIRI) are feasible. The principal benefit of the FOLFOXIRI regimen is its high RR; further, high liver resection rates have been reported. However, the toxicity of these drugs when given in combination results in dose reductions for each of the drugs [8, 10, 11].

The second strategy involves stop-and-go regimens such as the OPTIMOX series that include oxaliplatin-free intervals to reduce grade 3 sensory neuropathy [16]. This stop-and-go regimen avoided the problem of oxaliplatin-induced neurotoxicity by using a dose-intense FOLFOX7 regimen for a defined period, stopping the therapy before severe neurotoxicity developed, and later reintroducing the same regimen. This regimen was extremely useful for reducing the neurotoxicity of oxaliplatin; however, response and survival were not improved.

The third method involves alternating regimens such as 4 courses of FOLFOX and 4 courses of FOLFIRI, as investigated in this trial. To improve response and survival, other alternating regimens have been examined. Alternating oxaliplatin and irinotecan in association with the De Gramont regimen has been used in first- and second-line chemotherapy for metastatic colorectal cancer [17]. Seventy-nine patients with previously untreated, unresectable colorectal cancer were included in a study of this regimen as a first-line treatment. Treatment consisted of 5-FU/leucovorin plus oxaliplatin alternated biweekly with the same 5-FU/leucovorin regimen plus irinotecan. Treatment was maintained until tumor progression or unacceptable toxicity was noted. Grade 1 or 2 neurotoxicity was observed in 59% of cases, but no grade 3 and 4 neurotoxicity was observed. An objective RR of 54% was attained. The median time to progression and OS was 13

and 18 months, respectively. In another phase II study, GERCOR utilized an alternating regimen of 4 cycles of FOLFOX6 and 4 cycles of FOLFIRI (FIREFOX) as a second-line therapy in 39 patients with 5-FU-resistant unresectable colorectal cancer [18]. Eighteen patients had an objective response (46.1%). The median PFS and OS were 8.8 and 18.7 months, respectively. Only 2 patients (5.1%) exhibited grade 3 oxaliplatin-induced neuropathy. Another group evaluated an alternating XELFOX and XELFIRI regimen [19]. Treatment consisted of 2 consecutive days of 200 mg/m^2 leucovorin, 400 mg/m^2 5-FU and 2,000 mg/m^2 capecitabine in 1 cycle and the addition of 50 mg/m^2 oxaliplatin for 2 days before the combination treatment in the subsequent cycle.

To our knowledge, this study is the first to examine the efficacy and safety of an alternating regimen of 4 courses of FOLFOX6 followed by 4 courses of FOLFIRI in patients with non-pretreated metastatic colorectal cancer. The objective RR of 58.5% is better than that of the FOLFOX or FOLFIRI chemotherapy regimens without molecular targeting agents and is close to that of FOLFOXIRI chemotherapy [9]. This regimen might be a substitute for FOLFOXIRI which has a high rate of conversion to surgery. In our study, 9 (19.6%) patients were converted to surgery including liver resection. In addition, this strategy was implemented to increase the efficacy of treatment and extend survival. The median PFS and OS were 10.3 and 28.4 months, respectively. PFS for first-line FOLFOX6 or FOLFIRI treatment without molecular targeted agents was 8–10 months [1], and PFS increased to 10–14 months when second-line treatment was also administered. Therefore, PFS in this study was not long, although OS was extended. This survival may be partly influenced by the therapy that followed the treatment administered in the study. In this phase II study, because molecular targeted agents were not included in the protocol treatment, FOLFOX6 and FOLFIRI with molecular targeted agents were chosen as the second-line treatment. At present, oral fluoropyrimidine with molecular target agents were considered as a choice as a second therapy and the third therapy. Although survival was not a primary endpoint, the remarkably long OS associated with the FIREFOX regimen is noteworthy. Furthermore, the most remarkable result in this study was the low level of neurotoxicity. In particular, no grade 3–4 peripheral neurotoxicity was observed. Only 6 patients experienced grade 2 neurotoxicity. Figure 3 shows the occurrence of neurotoxicity in all patients. Neurotoxicity improved during the FOLFIRI cycles. This tendency was similar to that observed with the OPTIMOX regimen. However, the OPTIMOX regimen does not have a chemotherapy-free interval; therefore, PFS can be maintained well. In this phase II trial, only 6 (12.7%) patients did not receive FOLFIRI because of disease progression or patient refusal. The high usage rate for the 3 active drugs is advantageous for this regimen because 20–30% of patients cannot receive second-line chemotherapy because of disease progression. Therefore, this low level of neurotoxicity may have greatly contributed to the long PFS and OS in this study.

Our findings suggest that the alternating administration of 4 cycles of FOLFOX6 and 4 cycles of FOLFIRI (FIREFOX) is effective and well tolerated as a first-line treatment for metastatic colorectal cancer. A favorable toxicity profile and prolonged time to progression were observed. Based on this study, we recently conducted and finished another phase II study of 4 alternating cycles of FOLFOX6 and FOLFIRI with bevacizumab.

Disclosure Statement

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特集　臨床現場が知りたい大腸がん薬物治療

2．効果的な治療法の選択—専門医からのアドバイス

2）ファーストラインからベバシズマブを使用していくか？

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View Points !

▶ファーストラインの治療選択は，治療の目的をよく考える。
▶ファーストラインのベバシズマブの選択はエビデンスとガイドラインに則した選択である。
▶原発巣からの出血，全周性の狭窄病変の場合は併用を控える。
▶*KRAS* wild type 症例に対して，ベバシズマブと抗 EGFR 抗体のどちらが有用かについては，肝限局転移症例を含め結論が得られていない。

切除不能結腸・直腸がんの治療の目的

- ESMO のプラクティスガイドラインでは，図1のように症例を3つにグループ化して治療の目的を明確にした上で治療レジメンを選択する考え方が一般的になりつつある[1]。
- グループ1は「潜在的に切除の可能性のある転移巣（肝・肺転移）を有する場合」，グループ2は「切除不能の多発転移巣を有し，病勢進行が早い，腫瘍関連症状がある，もしくは腫瘍量が多い場合」，グループ3は「切除不能の転移巣を有し，症状がなく進行が緩徐である場合」である。
- グループ1，2では奏効率の高い化学療法，グループ3では副作用の少ない化学療法を選ぶべきであるという考え方ができ

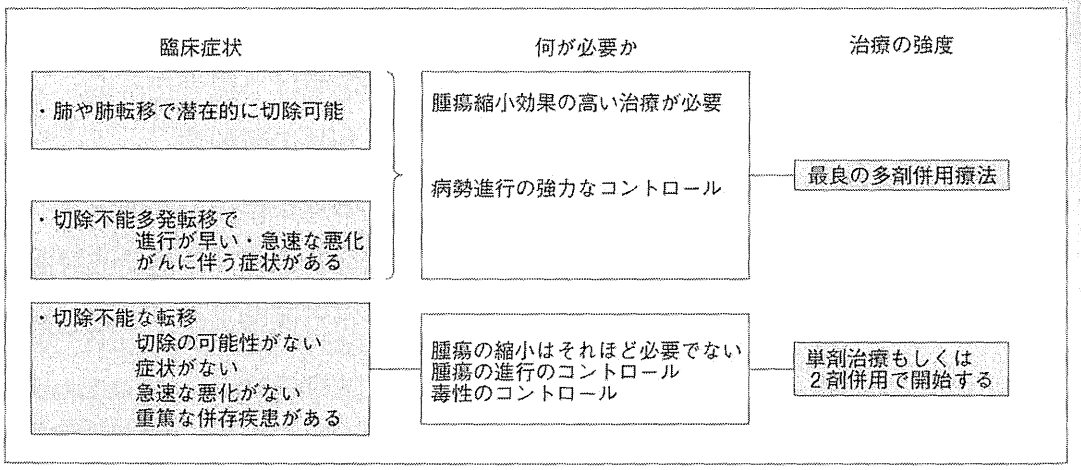

図1　ESMO のプラクティスガイドラインによる進行再発結腸・直腸癌の治療方針
（文献1）より改変）

表1 ファーストラインにおけるベバシズマブの主な治療成績

試験名	レジメン		RR（%）	PFS（month）	OS（month）
AVF2192g	5-FU/LV＋BEV	104	26 P=0.055	9.2 HR=0.50, P=0.0002	16.6 HR=0.79, P=0.16
	5-FU/LV	105	15.2	5.5	12.9
AVF2107g	IFL＋BEV	402	44.8 P=0.004	10.6 HR=0.54,	20.3 HR=0.66,
	IFL	411	34.8	6.2 P<0.001	15.6 P<0.001
NO16966	FOLFOX or XELOX ＋ BEV	699	38 P=0.99	9.4 HR=0.83, P=0.0023	21.3 HR=0.89, P=0.077
	FOLFOX or XELOX	701	38	8.0	19.9

RR: response rate, PFS: progression free survival, OS: overall survival, HR: hazard ratio

る。しかし各々の症例がどのグループであるのかの臨床的判断は難しい。

- 切除不能結腸・直腸がんの治療の目的は，一部の患者では治癒率の向上を目指す場合もあるが，ほとんどの場合，生存期間（OS）の延長，症状の緩和である。症例ごとの状況を考慮してレジメンを選択して治療を進める必要がある。

切除不能結腸・直腸がんに対するベバシズマブのファーストライン治療に関するエビデンス

- ベバシズマブ（BEV）はVEGFに対するキメラ型ヒト化IgG1モノクローナル抗体である。レセプターへのVEGFの結合を阻害して，血管新生を抑制して腫瘍の増大を抑える。また，腫瘍周囲組織の血行が再構築されるため，薬剤の腫瘍への移行や透過性が改善するとも考えられている。
- 表1はファーストライン治療におけるBEV使用のエビデンスである。AVF2192g試験はフルオロウラシル（5-FU）＋ホリナート（LV）療法に対するBEVの上乗せを検討した試験である[2]。Response rate（RR）は5-FU＋LV単独で15.2%，BEV併用群では26%であった。Progression free survival（PFS）のHRも0.5であり顕著な差を認める。
- その後行われたAVF2107g試験はIFL（イリノテカン＋5-FU＋LV）療法との併用で，奏効率，PFS, overall survival（OS）すべてで上乗せが認められている。当時はセカンドライン以降におけるクロスオーバーの症例がなかったとはいえ，OSでハザード比（HR）は0.66と明らかな差を認めた[3]。
- さらにNO16966はFOLFOX4もしくはXELOX療法との併用でBEVの上乗せを検討した試験である。この試験でもプライマリーエンドポイントのPFSにおいてBEVの上乗せが証明された[4]。
- これら臨床試験の結果からファーストライン治療におけるBEV併用の有用性が証明されてきた。つまり切除不能大腸がんのファーストライン治療にはBEVを併用した治療法のエビデンスがある。

ファーストライン治療にBEVを使用しない場合

- 表2は特定使用成績調査時におけるBEVの重篤な副作用である[5]。
- 頻度が低いとはいえ，出血や消化管穿孔などがあり得るため，全周性の原発巣が残存

表2 ベバシズマブの主な有害事象の報告

	G3異常の有害事象		
	特定使用成績調査(%)	First-BEAT(%)[9]	BRiTE(%)[10]
高血圧	0.4	0.5	16.4
出血	1.4	0.8	1.9
タンパク尿	<0.1	—	—
消化管穿孔	0.9	0.7	1.7
動脈血栓塞栓症	0.3	0.6	2.1
静脈血栓塞栓症	1.3	1.0	
創傷治癒遅延	0.3	0.3	1.2

(文献4)より改変)

し，腸閉塞症状や出血を認める場合は，原発巣への対処を行ってからBEVを使用すべきと考えられる。

- BEV使用後には創傷治癒の遅延も経験するため術後早期からのBEVの使用は慎重に考慮すべきである。
- 術後一定期間は分子標的治療薬を併用しないFOLFOX6やFOLFIRI療法を行うか，*KRAS*に変異がなければ抗EGFR抗体を使用することも視野に入れるべきである。

ファーストラインの治療選択とセカンドライン治療でのBEV継続投与

- ML18147試験はファーストラインにBEVを併用した標準的化学療法を行った後に，セカンドラインとしてBEVを継続的に併用する群と，化学療法のみの群を比較した第Ⅲ相試験である[6]。
- BEV併用群のOSは11.2ヵ月，BEV非併用群では9.8ヵ月，HRは0.81（95%信頼区間：0.69-0.94；p=0.0062）であり，有意にBEV併用群でOSの延長が認められた。PFSも，BEV群が5.7ヵ月，化学療法のみ群が4.1ヵ月，HRが0.68（95%信頼区間：0.59-0.78；p<0.0001）でBEV併用群の優越性が証明されている。そのほか，過去に行われたE3200試験でも，大腸がんのセカンドライン治療においてBEVの有用性が証明されている。
- サードライン以降にはセツキシマブ（Cmab）やパニツムマブ（Pmab）などの抗EGFR抗体が単独で効果を発揮することが報告されている。したがって長期の化学療法の継続を考えた場合，ファーストライン，セカンドラインにBEVを使用した治療を行い，サードライン以後に副作用の強い抗EGFR抗体などを行うという考え方もある。
- このようにセカンドライン以降のストラテジーを考えてファーストラインを選択することも大切である。

肝限局型転移に関するエビデンス

- 肝限局転移の治療は，切除を含めた集学的治療を行うことで根治を目指せることも少なくない。肝限局転移の治療方針を決定するうえで必要なのは，ESMOのプラクティスガイドラインでいえばグループ1であるかどうか，最終的に切除が可能かどうかである。
- 切除可能な肝転移症例を対象に行ったEORTC 40983試験では，術前にFOLFOX4療法を

行う群と手術単独群の比較を行っているが，切除可能肝転移に対する術前化学療法によるOSの延長は証明されていない[7]。

- したがって現時点では肝転移の切除が可能と判断されれば，切除を先行させてもよい。
- しかし両葉に多数の転移がある場合や肝内の重要脈管にがんの浸潤がある場合など，明らかに切除不能な場合は長期的に治療を継続する予定でファーストラインの化学療法を選択する。この場合BEVを選択することが合理的である。
- 治療の選択に議論があるのは，切除が最適かどうか判断の難しい病変である。そのような境界領域の病変では縮小効果が高い治療法ほど切除率が向上する。
- これまでのCRYSTAL試験，PRIME試験，OPUS試験などの抗EGFR抗体を使用した臨床試験の結果から勘案すれば，*KRAS*野生型の症例に限るとBEVに比較して抗EGFR抗体の方が縮小率の上乗せ効果が高い傾向にある。したがって，境界領域の病変にはBEVに変えて，抗EGFR抗体を選択してもよいと考えられる。

BEVと抗EGFR抗体の直接比較試験

- 肝限局転移にかかわらず，これまでにファーストライン治療としてBEVと抗EGFR抗体のどちらを使用すべきかについて明らかにした試験結果はない。
- ファーストラインとしてはBEVを使用することを基本としつつも，状況に応じて抗EGFR抗体を使用する場合もある。現在，複数のBEVと抗EGFR抗体を比較する試験が進行中である。
- CALGB/SWOG80405は*KRAS*野生型を対象としたFOLFOX/FOLFIRI＋BEV vs FOLFOX/FOLFIRI＋Cmabの直接比較試験である。
- PEAK試験はFOLFIRI＋BEV vs FOLFIRI＋Pmab，またFIRE-3試験はFOLFIRI＋BEV vs FOLFIRI＋Cmabを比較する試験であるが，この試験においては87例の*KRAS*変異症例に関するサブグループ解析の結果が既に報告されている[8]。
- プライマリーエンドポイントである奏効率はCmab群43.9%，BEV群47.8%（P＝0.83）であり，有意差は認めなかった。また，PFSにも差を認めていない。
- 前述したML18147試験でも*KRAS*変異症例においてはBEVも期待通りの効果を発揮しない可能性が示唆されている。今後の解析結果が大いに期待される。

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ORIGINAL ARTICLE

The treatment outcomes of synchronous and metachronous esophageal squamous cell carcinoma and head and neck squamous cell carcinoma

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Abstract
Background The treatment outcomes of patients with esophageal squamous cell carcinoma (ESCC) and head and neck squamous cell carcinoma (HNSCC) have been poorly documented.
Patients and methods We investigated 50 patients with synchronous and metachronous ESCC and HNSCC. We focused on the treatment results of 20 patients with synchronous ESCC and HNSCC who received simultaneous chemoradiotherapy (CRT).
Results There were 34 patients (68.0 %) with stage 0–I ESCC and 40 patients (80.0 %) with stage II–IV HNSCC. A total of 13 (26.0 %) patients underwent endoscopic mucosal resection and 28 (56.0 %) underwent CRT for ESCC, and 35 (70.0 %) of the patients with HNSCC were treated with CRT. The 5-year overall survival rates of the 50 patients with synchronous and metachronous ESCC and HNSCC was 57.8 %. For the 20 patients with synchronous ESCC and HNSCC who received simultaneous CRT, the CRT was completed in 19 (95.0 %) patients. Although grade 3–4 adverse events were observed in five (25.0 %) patients, there were no therapy-related deaths. Complete responses (CRs) of both ESCC and HNSCC were observed in ten (50.0 %) patients. The 5-year overall survival rate of the 20 patients was 60.0 %. CRs of both ESCC and HNSCC were obtained in seven (58.3 %) patients by using a cisplatin/5-FU regimen ($n = 12$), and in the other three (37.5 %) patients by a platinum-based monotherapy regimen ($n = 8$).
Conclusion The surveillance of double cancer and the use of radical treatment contributed to the favorable outcome of the patients with ESCC and HNSCC. The optimal chemotherapy regimen for simultaneous CRT remains to be determined.

Keywords Multiple cancer · Squamous cell carcinoma · Chemoradiotherapy · Surgery · Chemotherapy regimen · Prognosis

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Introduction

The occurrence of multiple primary cancers in the upper aerodigestive tract is a well-known phenomenon that has been ascribed to "field carcinogenesis." Both alcohol consumption and cigarette smoking are well-established risk factors for esophageal squamous cell carcinoma (ESCC), and these two factors have synergistic effects on the development of ESCC and squamous cell carcinoma of the head and neck (HNSCC) [1–8]. Therefore, careful attention should be paid to the diagnosis and during the treatment of ESCC and HNSCC in order to ensure that only one primary tumor is present.