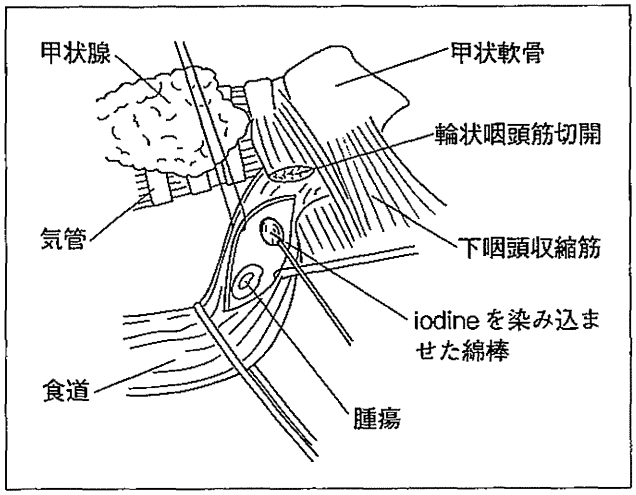


図1. 食道口側断端の術中診断と輪状咽頭筋切開（文献6より引用改変）
下咽頭収縮筋の輪状咽頭部切開により，口側に切除断端を延長する．

## Ⅱ．喉頭機能温存のための術前CRTの現状と成績

頸部食道癌においてCRTが行われる目的は，純粋に治療成績を向上させるためよりも，本来であれば咽喉頭頸部食道切除の適応である症例において，患者が喉頭温存を希望した場合に施行されることが多い．喉頭温存例の増加が，全体として生存率の向上につながっているという根拠はない[1]．しかし国内からの報告を参照すると，喉頭合併切除の適応例に対する術前CRTによって，喉頭温存可能例は増えているとされている[9,10]．その一方でサルベージ手術も増えている[11]．

## Ⅲ．治療の実際

### 1．術前CRT

『食道癌診断・治療ガイドライン』では，StageⅡ～Ⅲ食道癌に対してfluorouracil（5-FU）＋cisplatinを用いた術前化学療法が推奨されているが，切除可能食道癌に対する術前CRTについては，推奨するだけの十分な根拠がないとされている[1]．しかしながら，臨床の現場においては根治的CRTのプロトコルに準じ，5-FU＋cisplatinを中心とした薬剤に40 Gy程度の線量の照射を併用した術前CRTが試みられている．機能温存を目的とした頸部食道癌に対する術前CRTにおいても，同様のプロトコルが適応となると考えられる．使用薬剤は，JCOG9708における根治的CRTのプロトコルに基づいた5-FU 700 mg/m²/日×4日間およびcisplatin 70 mg/m²/日×1日間などのプロトコルが頻用されるが，docetaxelを加えた3剤併用療法や，nedaplatinを使用したプロトコルなども試みられている[1]．

照射野については，根治照射の場合『食道癌診断・治療ガイドライン』によると，中深頸リンパ節（No.102-mid）から気管分岐部リンパ節（No.107）までのいわゆるshort-T字型照射が標準的とされている．しかし，喉頭温存手術を念頭におく場合においては，リンパ節転移の状況によっては原発巣にしぼった照射野を採用している．

頸部食道癌における根治照射は，胸部食道癌の照射に比べ照射野が高位になるために，口腔内や咽頭の粘膜障害が重症化するとの報告がある[12]．術前照射を行う際にも同様の副作用が発生する可能性があり，注意が必要である．40 Gy終了時には，食道造影，上部消化管内視鏡検査，気管支鏡検査，頸部超音波検査，CT，fluorodeoxyglucose-positron emission tomography（FDG-PET）により，喉頭・気管への浸潤の解除の成否やリンパ節転移の状況，十分な口側食道の切除マージンの確保が可能かどうかを評価している[13]．この時点で，CRTにより完全奏効にいたる可能性が高い症例や，喉頭温存手術の基準を満たさない場合には根治照射を行い，遺残・再発例に対してはサルベージ手術を行っている．

仮に癌腫の縮小が得られた場合でも，根治性を保ちながら喉頭温存が可能か否かを術前に確実に判断するのは困難な場合も少なくない．また，近年では喉頭合併切除を回避できない場合でも，音声同時再建を伴った遊離腸管移植手術の報告もみられるため[14～16]，治療法の選択について，このような情報も提示したうえで十分に説明を行い，患者とよく話し合うことが必要である．

### 2．術前CRT後の手術

#### a）適　応

術前CRT後の喉頭温存手術の適応としては，①喉頭・気管への浸潤が解除されていること，②腫瘍の口側に切除のためのマージンが確保されていること，③郭清の根治度を落とさずに少なくとも片側の反回神経が確保されることといった条件を満たす必要がある．

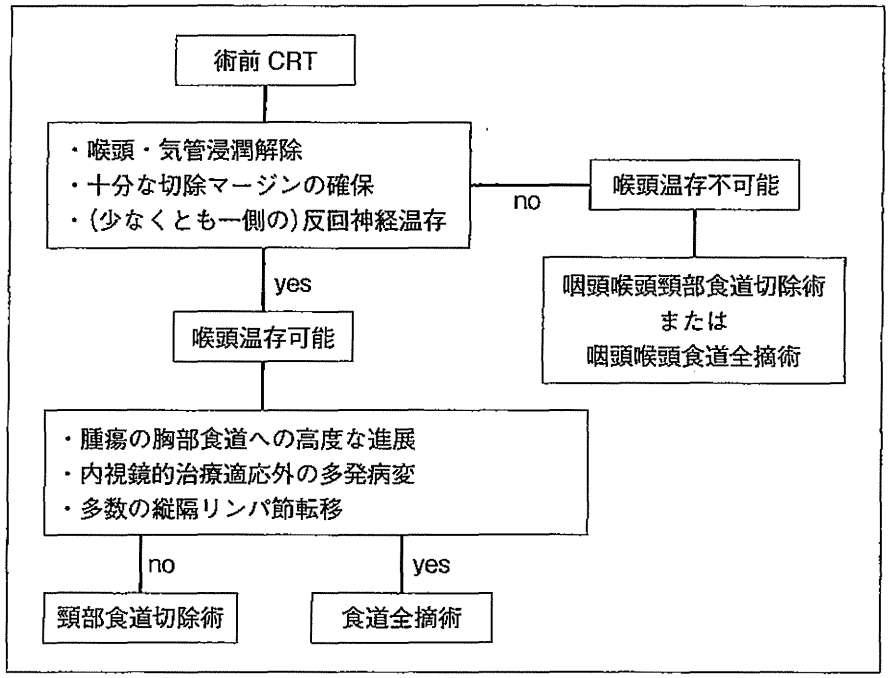


図2. 術式選択のフローチャート(文献7より引用改変)

表1. 再建法の比較(文献7より引用改変)

| | 遊離空腸間置 | 胃管再建 |
|---|---|---|
| 適　応 | 1. 原発巣が頸部食道にとどまる場合<br>2. 胸部食道の多発病変が内視鏡的切除の適応となる場合 | 1. 胸部食道への腫瘍進展が高度な場合<br>2. 胸部食道の多発病変に対して手術切除が必要な場合 |
| 利　点 | 1. 胸部食道の温存が可能で，嚥下消化機能に優れる<br>2. 比較的侵襲が少ない<br>3. 腹部手術の既往の影響は少ない | 1. 吻合箇所が少ない<br>2. 通常の食道癌手術における吻合技術で可能である |
| 欠　点 | 1. 顕微鏡下での微小血管吻合の技術を要する<br>2. 移植血管床への照射の影響や動脈硬化の程度によっては施行困難な場合がある | 1. 生理的な食道輸送能や胃の消化機能の消失<br>2. 胃切除の既往や，重複癌例では施行困難な場合がある |

b) 切除の実際

手術は40 Gyの照射終了後，約1ヵ月の間隔をおいて施行している．喉頭温存手術には，胸部食道切除の有無により喉頭温存頸部食道切除術と喉頭温存食道全摘術とがある．腫瘍の進展が胸部食道に及ぶ場合や，内視鏡的切除の適応とならない多発病変，多くの縦隔リンパ節転移がみられる場合に胸部食道を合併切除することがある[1]．頸部食道癌では，腫瘍の進展が食道入口部に近い場合や狭窄例では，手術前に腫瘍進展範囲が正確に診断できないことも多い．こうした症例では，術中に食道を切開して粘膜面を露出しiodine染色により口側断端を確認する方法[6]や，切除断端の術中迅速病理診断を用い，腫瘍進展範囲を診断する必要がある[1,13]．頸部食道を口側に輪状軟骨下縁付近まで剝離すると，その外側は下咽頭収縮筋におおわれている．この輪状咽頭部を切開することで咽頭空腸吻合の縫い代を稼ぐことができる．また，狭窄を拡張する効果により誤嚥を減少させる(図1)[6,8]．当科における，術中所見も含めた最終的な術式選択のフローチャートを図2に示す．

c) 再建法の選択

本邦では，遊離腸管移植による再建が一般的であり，第一選択とされている[1]．一方，欧米では

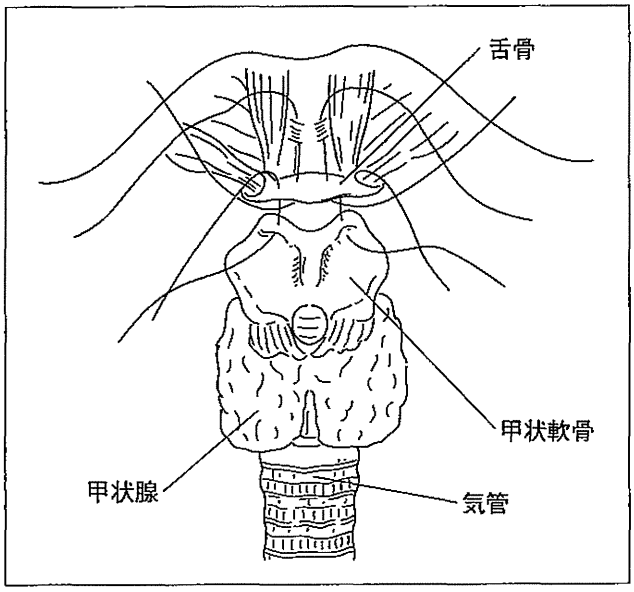


図3. 喉頭挙上術

胃管による再建は比較的合併症が少なく，早期に経口摂取が可能であり比較的好ましいという報告が多く，選択されうる再建方法であるとされる[1]．遊離腸管移植と胃管再建の主な二つの再建法の比較を表1に示す．胸部食道の切除を追加する場合は，胃または結腸を用いて再建を行うが，口側への距離が不十分な場合には遊離空腸移植を付加することもある[1]．術式および再建臓器の選択が多岐にわたるため，これにかかわる諸臓器は術前に十分な精査がなされている必要があるが，主病巣より肛門側の食道や胃病変については，狭窄などにより術前評価が困難な場合がある．このような症例に対しては，術中に腫瘍肛門側の食道壁に小切開を加えて内視鏡を挿入し，食道，胃の観察を行っている[2]．

d) 喉頭挙上術

喉頭温存手術の後，誤嚥により経口摂取が困難となることも多いため，われわれは全例に喉頭挙上術を併施している（図3）．具体的には甲状軟骨と舌骨，舌骨と舌骨上筋ないし下顎骨とを縫縮し，喉頭を挙上している．これにより誤嚥の減少と比較的早期からの経口摂取が可能になる[2~7]．

e) 喉頭温存手術に際しての留意点

喉頭温存術式を選択するうえで留意すべき点は，①喉頭が温存されるため，喉頭合併切除と比し消化管吻合や血管吻合に要するワーキングスペースが狭小化すること，②反回神経周囲や気管周囲が広範に剝離されることが多いため，術後反回神経麻痺による喉頭機能の低下が懸念されることである[17]．①については，特に再建時に問題とされる．口側食道と再建臓器との吻合時には，気管を十分に挙上してスペースを確保し，より慎重な吻合操作を行うことが求められる．また遊離空腸間置においては，術前照射の影響によっては移植床血管の変性のために血管吻合が困難な場合が生じることも想定しておく．②については，術前治療により喉頭温存が達成されたにもかかわらず，特に咳嗽反射や嚥下機能が低下している高齢者において術後の嗄声や誤嚥によって十分なQOLが得られない場合があることも指摘されており[18]，手術適応を決めるうえで考慮されるべき点といえる．また喉頭温存術後の嚥下障害は術後合併症の大きな問題の一つであり，われわれは先に述べたような喉頭挙上術を施行している（図3）．その他の合併症としては，反回神経麻痺などによる声門狭窄があげられ，術中の繊細な手技と術後の慎重な呼吸管理が肝要である．

## おわりに

頸部食道周囲には重要臓器が多く，特に喉頭合併切除による発声機能の喪失は重大なQOLの低下をもたらすものである．頸部食道癌に対する術前CRTにより喉頭温存が可能な症例の増加が期待されるが，その一方でサルベージ手術が増加している．根治性を損なわず，なおかつ発声や嚥下といった喉頭機能を温存するためには，治療適応の慎重な検討と，複雑な解剖学的特性を十分に理解したうえでの細心の手術手技，厳重な術後管理が必要である．

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ORIGINAL ARTICLE—ALIMENTARY TRACT

# Intragastric administration of rikkunshito stimulates upper gastrointestinal motility and gastric emptying in conscious dogs

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**Abstract**
*Background* Traditional Japanese medicine, known as Kampo medicine, consists of mixtures of several medicinal herbs widely used to treat upper gastrointestinal disorders in Japan. Rikkunshito, one of these medicines, has not been evaluated with respect to its influence on gastrointestinal motor activity. We investigated the effect of rikkunshito on upper gastrointestinal motility and plasma ghrelin concentrations in conscious dogs.
*Methods* Contractile response to intragastric administration of rikkunshito was studied via surgically implanted force transducers. A powdered extract of rikkunshito (1.3, 2.7, and 4.0 g) dissolved in water was administered into the stomachs of normal and vagotomized dogs before feeding and gastric emptying was evaluated. Several inhibitors of gastrointestinal motility (atropine, hexamethonium, and ondansetron) were injected intravenously before intragastric administration of rikkunshito. Plasma acylated ghrelin levels after intragastric administration of rikkunshito were measured.
*Results* In a fasting state, intragastric administration of rikkunshito induced phasic contractions in the duodenum and jejunum in normal dogs. Rikkunshito-induced contractions were inhibited by atropine, hexamethonium and ondansetron. In vagotomized dogs, rikkunshito induced phasic contractions, similar to normal dogs. Gastric emptying was accelerated by intragastric administration of rikkunshito in a dose-dependent manner. The plasma acylated ghrelin level 150 min after intragastric administration of 4.0 g of rikkunshito was significantly higher than the control value.
*Conclusions* Intragastric administration of rikkunshito stimulates gastrointestinal contractions in the interdigestive state through cholinergic neurons and 5-HT type 3 receptors. Moreover, rikkunshito increases plasma acylated ghrelin levels. Rikkunshito may alleviate gastrointestinal disorders through its prokinetic effects.

**Keywords** Rikkunshito · Gastrointestinal motility · Gastric emptying · Ghrelin

## Introduction

Kampo medicine is the Japanese adaptation of traditional Chinese medicine and has been used in Japan for more than 1000 years. Kampo drugs include several medicinal herbs. The components of traditional Japanese medicine may have pharmacological effects that improve illness and the maintenance of a "natural balance". Traditional Japanese medicine is widely prescribed in Japan, and is fully incorporated into the modern health care system.

Rikkunshito is a traditional Japanese medicine used to treat a variety of gastrointestinal symptoms, such as abdominal fullness, bloating, nausea, vomiting, and postprandial early satiety. In Japan, rikkunshito is widely used to treat upper gastrointestinal disorders, including functional dyspepsia (FD) [1, 2], gastroesophageal reflux (GER) [3–5], dyspeptic symptoms of postgastrointestinal surgery [6, 7], and chemotherapy-induced nausea [8]. Animal

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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

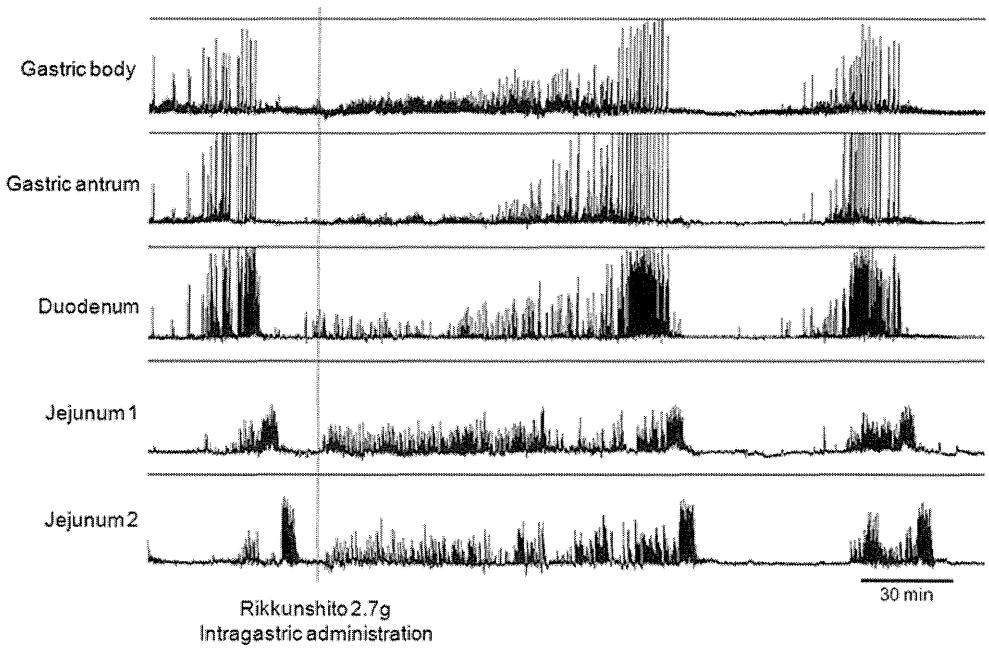


**Fig. 1** Effects of intragastric administration of rikkunshito on gastrointestinal motility during the interdigestive state in the normal group. Rikkunshito induced phasic contractions lasting for about 30 min in the duodenum and jejunum

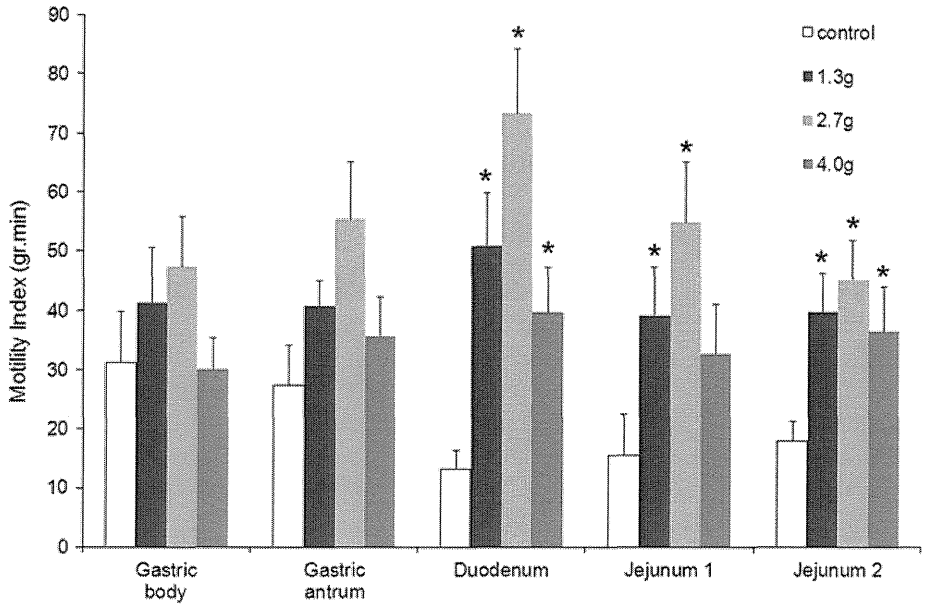


**Fig. 2** The MI for 30 min after intragastric administration of rikkunshito. The MI of rikkunshito-induced contractions in the duodenum and jejunum increased in a stepwise fashion up to a dose of 2.7 g. A higher dose of 4.0 g of rikkunshito did not augment this effect

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).

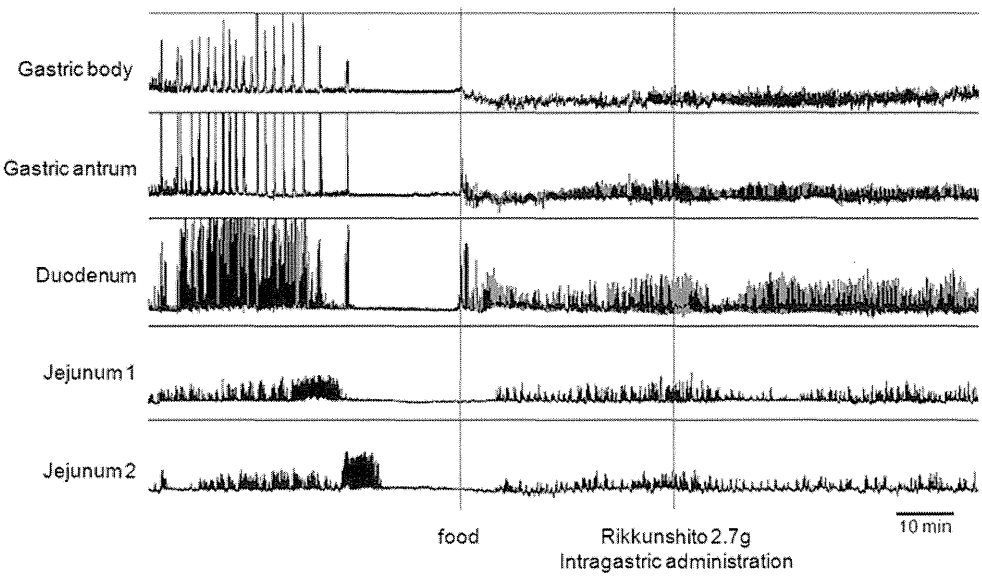


**Fig. 3** Effects of rikkunshito on upper gastrointestinal motility in the fed state. After food intake, the fasting motor pattern was immediately disrupted and replaced by the fed motor pattern, characterized by irregular, high-frequency contractions. Rikkunshito had no significant effect on the fasted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

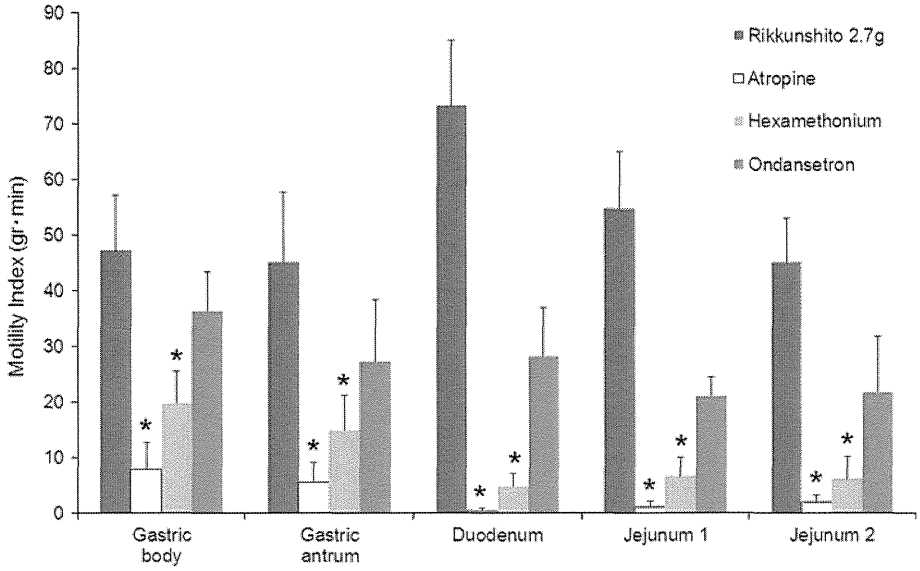


**Fig. 4** Effects of antagonists on the MI for 30 min during the motor response induced by intragastric administration of 2.7 g rikkunshito. Atropine and hexamethonium significantly inhibited the upper gut MI of rikkunshito-induced contractions at all sites

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).

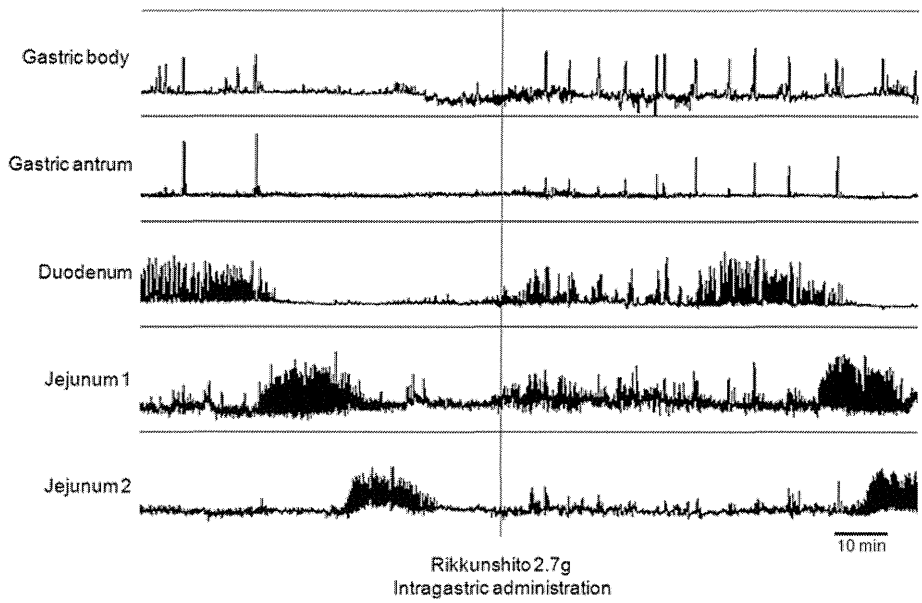


**Fig. 5** Effects of intragastric administration of rikkunshito on gastrointestinal motility during the interdigestive state in the truncal vagotomy group. Intragastric administration of rikkunshito induced phasic contractions in the duodenum and jejunum, as observed in the normal group

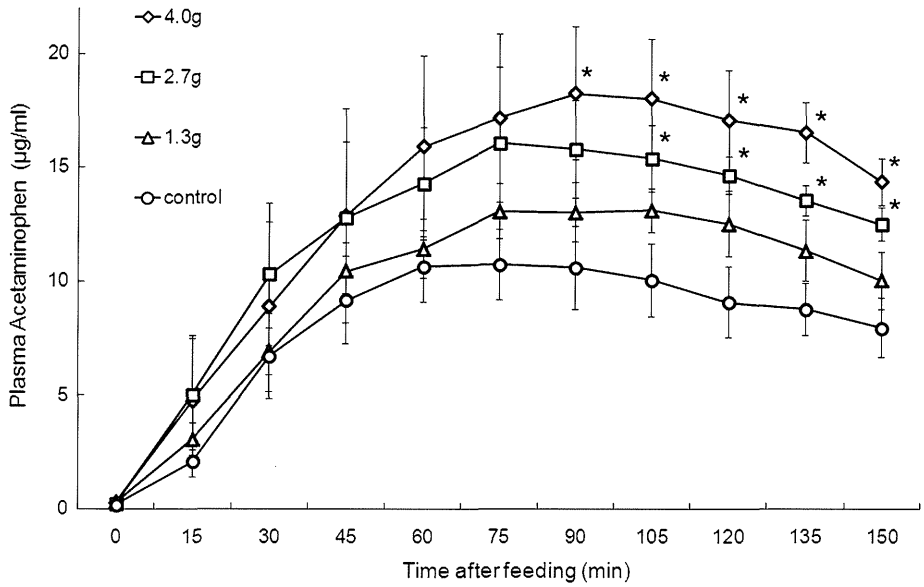


**Fig. 6** Effects of intragastric administration of rikkunshito on gastric emptying. Rikkunshito accelerated gastric emptying in a dose-dependent manner and 2.7 and 4.0 g of rikkunshito significantly accelerated gastric emptying as compared with the control

## 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.

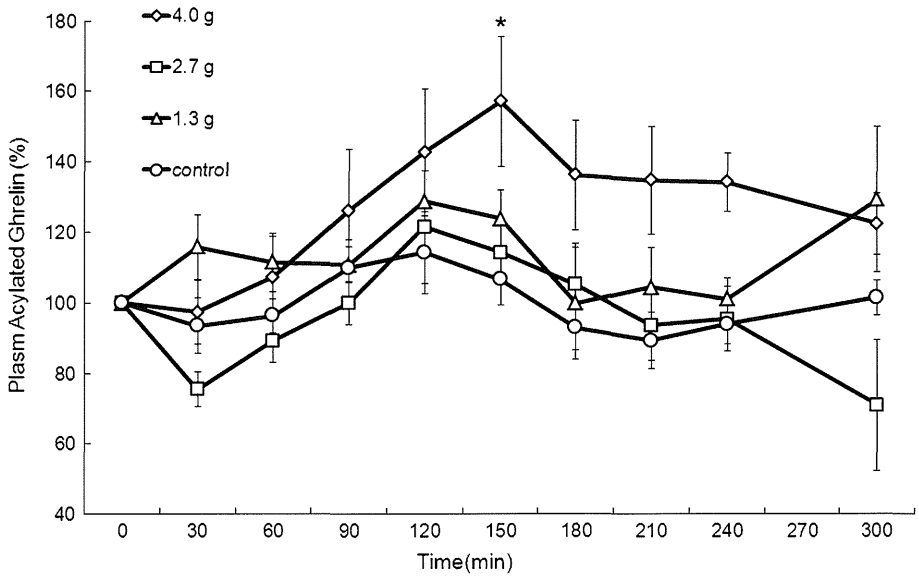


**Fig. 7** Effect of rikkunshito on plasma acylated ghrelin concentrations. After administration of 4.0 g of rikkunshito, plasma acylated ghrelin levels gradually increased, and the increase 150 min after administration was highly significant as compared with that in the control group

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

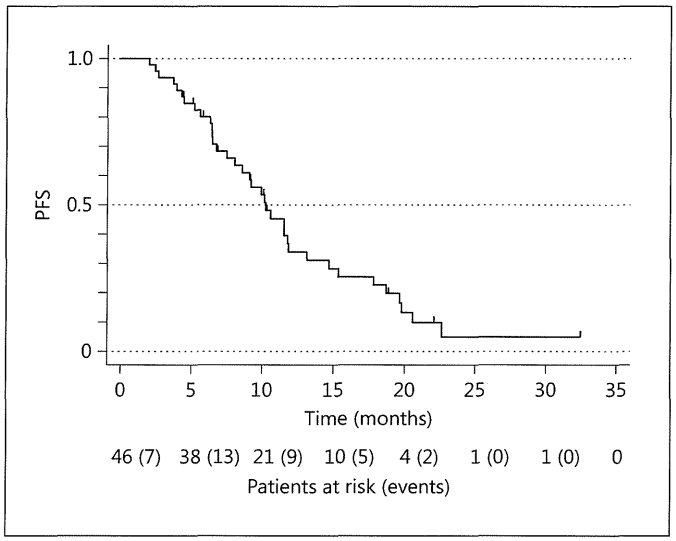


**Fig. 1.** Progression-free survival.

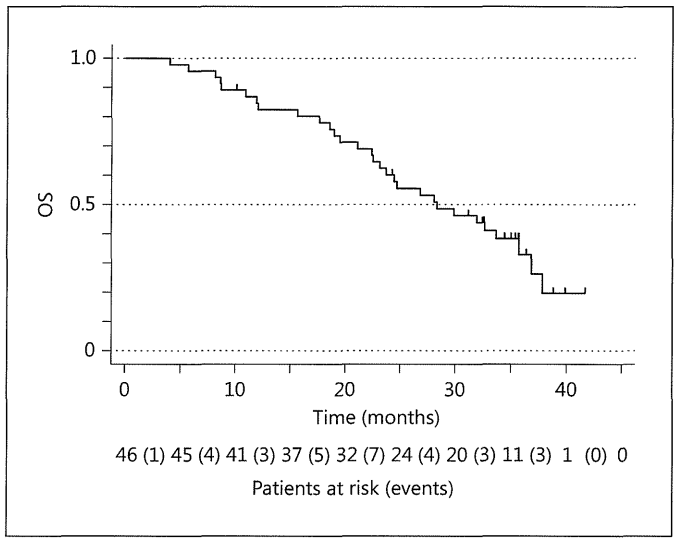


**Fig. 2.** Overall survival.

**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%

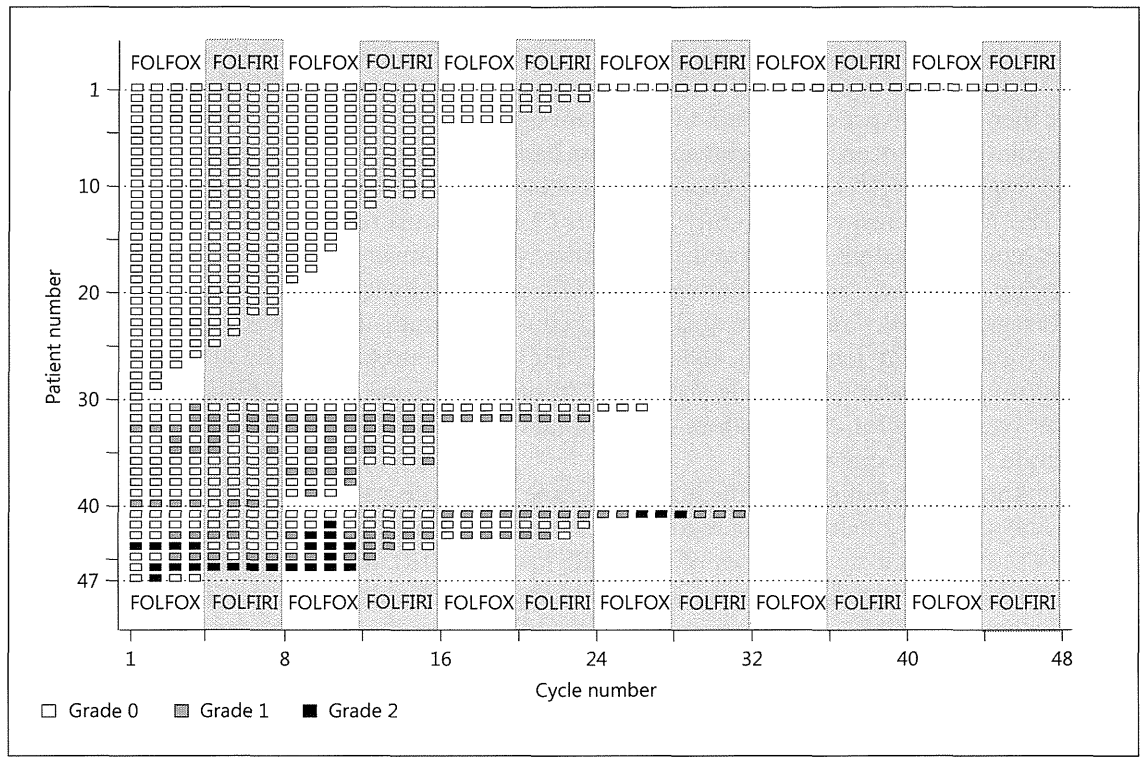


**Fig. 3.** Occurrence of neurotoxicity (CTCAE) in each cycle for all 47 patients. White squares indicate no toxicity; gray squares indicate grade 1 neurotoxicity; black squares indicate grade 2 neurotoxicity.

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

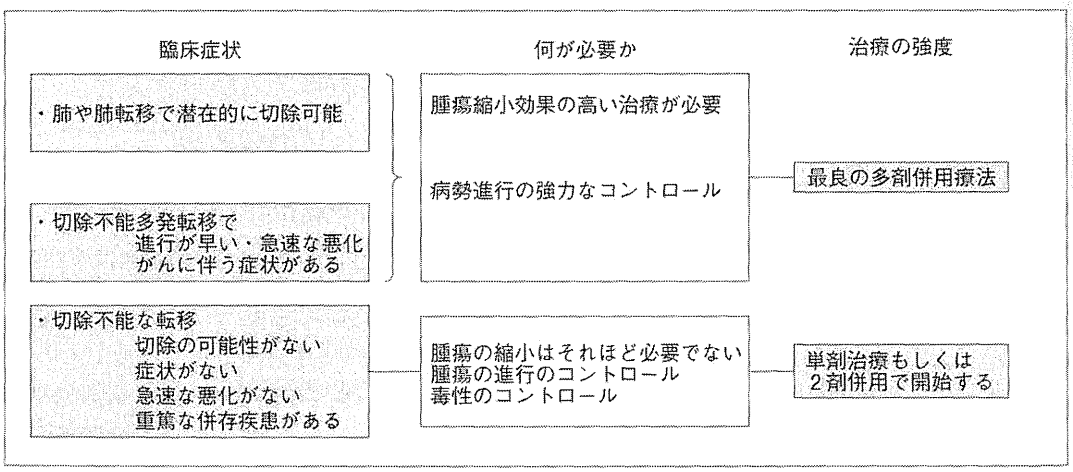


図1 ESMO のプラクティスガイドラインによる進行再発結腸・直腸癌の治療方針
（文献1）より改変）