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## The effects of rikkunshito on body weight loss after esophagectomy

Masaki Nakamura, MD, Mikihiro Nakamori, MD, Toshiyasu Ojima, MD, Masahiro Katsuda, MD, Keiji Hayata, MD, Makoto Iwahashi, MD, and Hiroki Yamaue, MD\*

Second Department of Surgery, Wakayama Medical University, School of Medicine, Wakayama, Japan

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### ABSTRACT

**Background:** After esophagectomy, esophageal cancer patients suffer from malnutrition, anorexia, and dysfunction of digestion and absorption. Rikkunshito, a traditional Japanese herbal medicine, reportedly attenuates gastrointestinal symptoms and appetite loss after gastrointestinal surgery. We evaluated the clinical effect of rikkunshito and its relationship with ghrelin in esophageal cancer patients after esophagectomy.

**Methods:** This prospective nonrandomized study included 40 patients with esophageal cancer who underwent esophagectomy at Wakayama Medical University Hospital. They were assigned to either the control group ( $n = 20$ , April 2011–January 2012) or the rikkunshito group ( $n = 20$ , January 2012–August 2012). Patients in the rikkunshito group received 2.5 g of rikkunshito before every meal for 48 wk beginning 4 wk after surgery. During the 48-week treatment, we assessed body weight loss, nutritional parameters, and quality of life (Functional Assessment of Cancer Therapy–Esophageal scale). The primary end point was the rate of body weight loss in two groups after the 48-week treatments.

**Results:** The rate of body weight loss was significantly less in the rikkunshito group than in the control group ( $P = 0.016$ ). The acyl ghrelin level after the 48-week treatments was significantly higher in the rikkunshito group ( $131.7\% \pm 74.5\%$ ) than in the control group ( $75.6\% \pm 47.5\%$ ,  $P = 0.039$ ). For the Functional Assessment of Cancer Therapy–Esophageal symptom scale, satisfaction of food consumption in the rikkunshito group was significantly better than in the control group at 52 wk postoperatively ( $P = 0.031$ ).

**Conclusions:** For esophageal cancer patients after esophagectomy, rikkunshito is useful for improving body weight loss in connection with an increase in plasma acyl ghrelin levels.

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### Introduction

As the prognosis of patients with esophageal cancer has improved in recent years because of advances in treatment, including perioperative chemotherapy, it is necessary to improve the quality of life (QOL) for these patients. In a recent

population-based study of esophageal cancer surgery, two-thirds of patients had lost more 10% of their preoperative body weight within 6 mo of surgery, and one in five had lost more than 20%.<sup>1</sup> Body weight loss and malnutrition are a considerable problem after esophagectomy and has been linked to appetite loss, eating difficulties, odynophagia, a

\* Corresponding author. Second Department of Surgery, Wakayama Medical University, School of Medicine, 811-1 Kimiidera, Wakayama 641-8510, Japan. Tel.: +81 73 441 0613; fax: +81 73 446 6566.

E-mail address: [yamaue-h@wakayama-med.ac.jp](mailto:yamaue-h@wakayama-med.ac.jp) (H. Yamaue).

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decrease in oral intake due to early satiety, a decrease in gastric acid production, neoadjuvant therapy, and female gender.<sup>1,2</sup>

Rikkunshito, a traditional Japanese herbal medicine, was reported to improve gastric emptying in patients with functional dyspepsia<sup>3,4</sup> and in patients who underwent proximal gastrectomy.<sup>5</sup> Recently, rikkunshito was reported to increase food intake and body weight in a rat anorexia model induced by administration of cisplatin.<sup>6</sup> Administration of rikkunshito has been shown to enhance the secretion of acyl ghrelin (i.e., the activated form of ghrelin) in rats,<sup>6</sup> and it was also reported to improve symptoms in patients with functional dyspepsia, accompanied by an increase in the plasma ghrelin levels.<sup>7</sup> However, there have been no studies investigating the clinical effect of rikkunshito and its relationship with ghrelin levels for esophageal cancer patients after esophagectomy.

Ghrelin is a 28-amino-acid peptide that is mainly secreted from the X/A-like cells in the gastric fundus, and several other tissues including the brain, duodenum, jejunum, and lung.<sup>8</sup> It acts as a natural ligand for the growth hormone secretagogue receptor and plays a role not only in growth hormone secretion<sup>8</sup> but also in initiating feeding as an appetite stimulant.<sup>9</sup> Ghrelin has two major molecular forms: acyl ghrelin and des-acyl ghrelin. Acyl ghrelin is thought to be an active form that specifically stimulates the release of growth hormone from the pituitary, as well as gastric motor activity and food intake.<sup>8</sup> Des-acyl ghrelin has opposing effects, decreasing food intake, and delaying gastric emptying.<sup>10</sup> Therefore, an increase in acyl ghrelin level and a decrease in des-acyl ghrelin level may be a favorable response that improves nutritional status and QOL in patients after gastrointestinal surgery. The plasma ghrelin level decreases immediately after gastrectomy and recovers gradually thereafter. However, recovery is poor after both total gastrectomy and proximal gastrectomy<sup>11</sup> because ghrelin-secreting X/A-like cells are abundant in the gastric fundus.<sup>12</sup>

The aim of the present study was to investigate the safety and efficacy of rikkunshito for esophageal cancer patients after esophagectomy. Moreover, we evaluated the clinical effects of rikkunshito on body weight loss, QOL, and plasma ghrelin levels for these patients.

## Patients and methods

### Patients

Forty consecutive patients with thoracic esophageal cancer who underwent an esophagectomy from April 2011 to August 2012 at Wakayama Medical University Hospital (WMUH) in Japan were enrolled preoperatively in this study. The consecutive patients in the first half of the study registration period were assigned to the control group ( $n = 20$ , April 2011-January 2012), and they in the latter half were assigned to the rikkunshito group ( $n = 20$ , January 2012-August 2012). In the control group, patients were managed without rikkunshito or a placebo postoperatively. In the rikkunshito group, patients received 2.5 g of rikkunshito before every meal for 48 wk beginning 4 wk after the surgery. Patients were not blinded for their postoperative treatment.

### Study design

This trial was designed as a prospective nonrandomized study. This trial was approved by the Ethical Committee on Clinical Investigation of WMUH and registered at UMIN-CTR ID #000006966 ([www.umin.ac.jp/ctr/](http://www.umin.ac.jp/ctr/)). Informed consent was obtained from all participating patients preoperatively, and they also agreed to follow-up for at least 52 wk after surgery. Inclusion criteria were: (1) thoracic esophageal cancer patient who would undergo radical transthoracic esophagectomy with gastric tube reconstruction; (2) aged 20-85 years; (3) performance status 0-2 according to Eastern Cooperative Oncology Group criteria<sup>13</sup>; and (4) appropriate informed consent obtained. Exclusion criteria were: (1) severe comorbidity, such as myocardial infarction, respiratory disorder requiring oxygen inhalation, liver cirrhosis, or chronic renal failure requiring hemodialysis; (2) the presence of other organ malignancies; (3) inability of oral intake; (4) patients who took Japanese herbal medicine within 2 wk before rikkunshito treatments; (5) a history of hypersensitivity to any Japanese herbal medicine preparation; (6) female patients who were pregnant, desiring pregnancy, or breastfeeding; and (7) patients who were diagnosed as inappropriate for this study by a physician.

During the 48-week rikkunshito treatment, the following parameters were assessed: body weight loss, nutritional parameters (albumin, prealbumin, transferrin, acyl ghrelin, and des-acyl ghrelin), and QOL based on the Functional Assessment of Cancer Therapy-Esophageal (FACT-E) scale.

### Rikkunshito

Rikkunshito (Tsumura & Co, Tokyo, Japan) is a granular preparation of a mixture of eight crude drugs, *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%), that is extracted with hot water. It has been approved for medicinal use by the Japanese Ministry of Health and Welfare, and its quality has been controlled by the Japanese Pharmacopoeia and the Japanese Herbal Medicine Codex (JHMC, non-Japanese Pharmacopoeia crude drug standards).

### Surgical procedures

All patients underwent radical esophagectomy with a two- or three-field lymph node dissection via a cervicothoracoabdominal approach. A right transthoracic procedure was performed via thoracotomy or thoracoscopy. All patients underwent esophageal reconstruction using stomach to replace the esophagus. In all patients, a gastric conduit through the retrosternal route or the posterior mediastinum was used to reconstruct the anastomosis with the cervical esophagus.

### Neoadjuvant therapy and adjuvant therapy

Beginning in 2005, our institution administered neoadjuvant chemotherapy for patients with clinical lymph node metastases and neoadjuvant chemoradiotherapy for patients with clinical T4 lesions. Nine patients in each group received neoadjuvant therapy. Among them, eight patients in each group

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