Clinical Trial Note

A randomized controlled Phase II/III study comparing endoscopic balloon dilation combined with steroid injection versus radial incision and cutting combined with steroid injection for refractory anastomotic stricture after esophagectomy: Japan Clinical Oncology Group Study JCOG1207

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Abstract

A randomized Phase II/III trial commenced in May 2014. Endoscopic balloon dilation with steroid injection is the current standard treatment for patients with refractory anastomotic stricture after esophagectomy. The purpose of this study is to confirm the superiority of radial incision and cutting with steroid injection in terms of both restricture-free survival and number of dilations within 24 weeks compared with endoscopic balloon dilation with steroid injection for these patients. A total of 130 patients will be accrued from 30 Japanese institutions over 3 years. The primary endpoint in the Phase II part is proportion of Grade 3/4 intraoperative hemorrhages, post-operative esophageal perforations, esophageal hemorrhages, pneumothorax, lung or mediastinum infections or other unexpected adverse events. Co-primary endpoints in the Phase III part are restricture-free survival and number of dilations within 24 weeks after treatment. Secondary endpoints are proportion of patients with anastomotic diameter >10 mm at 8 weeks after treatment, proportion of adverse events, proportion of patients experiencing improvement of dysphagia score at 2, 4, 8 and 24 weeks after treatment and proportion of patients with dysphagia score ≤1 at 24 weeks after treatment. This trial has been registered in the UMIN Clinical Trials Registry as UMIN000014017 [http://www.umin.ac.jp/ctr/index.htm].
Introduction

Esophageal cancer is the fifth most common cause of cancer-related death for men and the eighth for women worldwide (1) and esophagectomy is the standard treatment for a cure. Anastomotic strictures after esophagectomy occur in 5–46% of patients (2–3), which are mainly caused by the use of a circular stapler, ischemia of the upper part of the gastric tube and post-operative complications such as leakage, bleeding and infection of the anastomotic site (4,5). Patients with anastomotic strictures suffer from severe dysphagia.

Generally, endoscopic balloon dilation (EBD) or dilation with a bougie is indicated for anastomotic stricture after esophagectomy (6). For ∼40% of the patients with anastomotic stricture after esophagectomy, 1–3 dilations are sufficient to relieve their symptoms. However, 60% of the patients with anastomotic stricture suffer from severe dysphagia due to strictures that are refractory to repeated dilations more than three times (7). Thus, effective treatment for refractory anastomotic stricture has been required.

Adding steroid injection to anastomotic stricture after EBD or bougienage has been reported as one of the effective methods to treat refractory anastomotic strictures. Although this approach is still under discussion due to a lack of confirmatory randomized controlled trials (8–11), it has been commonly used and considered acceptable as the current standard treatment by the Gastrointestinal Endoscopy Study Group (GIESG) of the Japan Clinical Oncology Group (JCOG).

Furthermore, some groups have recently reported the usefulness of electrocautery treatment for anastomotic stricture after esophagectomy (12–15). The technique introduced in these electrocautery treatment reports is radial incisions. On the other hand, Muto et al. originally developed a new electrocautery method called the radial incision and cutting (RIC) method (16). The RIC method is characterized by cutting away the fibrotic tissue to maintain a wider lumen after performing radial incisions with an insulated-tip (IT) knife. Muto et al. (17) retrospectively assessed the efficacy of RIC in patients with refractory anastomotic stricture after esophagectomy and showed that the proportions of restrict-free survival at 6- and 12-month in the RIC group were higher than those in the historical control group of EBD (65.3% vs. 19.8%; 61.5% vs. 19.8%, respectively). As for safety, microperforation cured without surgical intervention was observed in 2.5% of the patients, but no other severe adverse events were observed.

Submucosal defect occurs after endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) for esophageal cancer. A circumferential extent of submucosal defect >3/4 increases the risk of stricture after EMR or ESD because of excessive formation of scar tissue. Circumferential submucosal defect is also caused by RIC. Therefore, in the report by Muto et al. (17), preventive EBD not to develop restructure was indicated once per week to maintain patency until the submucosal defect became a scar. On the other hand, Hanaoka and Hashimoto reported that steroid injection for mucosal defect is effective to prevent stricture after ESD of esophageal cancer (18,19). Steroid injection is less invasive and cheaper than repetitive EBD, so it has already been introduced into daily practice after ESD. On the basis of these advantages, it is assumed that steroid injection is also effective after RIC and can be an alternative method to preventive EBD.

Against this background, we are conducting a multicenter randomized Phase II/III trial to confirm the superiority of RIC with steroid compared with EBD with steroid in patients with refractory anastomotic stricture after esophagectomy. Before proceeding to the Phase III part, we evaluate the safety of RIC with steroid injection in the Phase II part because RIC is a relatively new technique only performed at limited institutions, and the safety and efficacy of RIC combined with steroid injection have not been assessed.

The JCOG Protocol Review Committee approved this study protocol in March 2014 and patient enrollment began in May 2014. Approval was obtained from the Institutional Review Board prior to starting patient accrual at each institution. This trial has been registered at the UMIN Clinical Trials Registry as UMIN000014017 [http://www.umin.ac.jp/ctr/index.htm].

Protocol digest of JCOG1207

Objectives

The aim of this study is to confirm the superiority of RIC with steroid injection in terms of both restrict-free survival and number of dilations within 24 weeks compared with EBD with steroid injection in patients with refractory anastomotic stricture after esophagectomy.

Study setting

A multi-institutional two-arm open label randomized Phase II/III study.

Endpoints

The primary endpoint in the Phase II part is proportion of Grade 3/4 intraoperative hemorrhages, post-operative esophageal perforations, esophageal hemorrhages, pneumothorax, lung or mediastinum infections, or other unexpected adverse reactions. Co-primary endpoints in the Phase III part are restrict-free survival and number of dilations for 24 weeks after treatment. Restrict-free survival is defined as days from randomization to either dysphagia score ≥2 with an inability to pass a standard endoscope with a diameter of 10 mm or larger through the stricture site, performing EBD for any reason, or death from any cause. It is censored at the last day when the patient is free from restrict or the day when local recurrence or secondary cancer is observed within 2 cm from the center of the stricture. The number of dilations for 24 weeks includes dilations for any reason. The secondary endpoints are proportion of patients with anastomotic diameter >10 mm at 8 weeks after treatment, proportion of adverse events, proportion of patients experiencing improvement of dysphagia score at 2, 4, 8 and 24 weeks after treatment and proportion of patients with dysphagia score ≤1 at 24 weeks after treatment. Dysphagia score is defined as follows: 0, able to eat a normal diet; 1, unable to swallow certain solids; 2, able to swallow semisolids; 3, able to swallow liquids only and 4, unable to swallow liquids.

Eligibility criteria

When a patient has anastomotic stricture after esophagectomy, the inclusion criteria of first registration are confirmed and informed consent is given. If the patient agrees to participate in the first registration, then endoscopic examination is undertaken. When the presence of anastomotic stricture, following the inclusion criteria of the second registration, is confirmed by endoscopy, the patient is randomized as the second registration process. By this process, only patients with

Key words: endoscopic balloon dilation (EBD), radial incision and cutting (RIC), anastomotic stricture, steroid injection
objective stricture are enrolled, and a patient randomized to the EBD arm can receive EBD with steroid injection right after the endoscopic examination.

When the presence of anastomotic stricture has already been confirmed by endoscopic examination performed within 28 days before first registration, the patient can meet the criteria of second registration at the same time. The patient is randomized to either the EBD arm or the RIC arm without additional endoscopic examination.

**Inclusion criteria for first registration**

(i) Meet all the following criteria regarding surgery for esophageal cancer:

(a) Subtotal esophagectomy for thoracic esophageal cancer performed.

(b) No finding of recurrence.

(c) Gastric tube reconstruction.

(d) No residual tumor.

(ii) EBD or bougienage for anastomotic stricture was performed more than twice before 24 weeks. If dilations were performed twice or more within 6 days, dilation was counted as one session.

(iii) No prior history of endoscopic incision for anastomotic stricture.

(iv) Dysphagia score ≥2.

(v) Stricture length ≤2 cm diagnosed by endoscopy or X-ray fluoroscopy.

(vi) No post-operative chemotherapy for esophageal cancer within 28 days before registration.

(vii) No prior history of radiotherapy for recurrence after esophagectomy or pre-operative radiotherapy of >60 Gy.

(viii) No prior history of chemotherapy for any cancer within 28 days before registration.

(ix) No plan for chemotherapy within 24 weeks after registration.

(x) Age ≥20.

(xi) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.

(xii) Sufficient organ function.

(xiii) Written informed consent.

**Inclusion criteria for second registration**

Patients are eligible for second registration when the presence of anastomotic stricture is confirmed by endoscopic examination performed within 28 days before second registration. The presence of anastomotic stricture is defined as the situation in which an endoscope for routine examination (diameter, 9.6–10.4 mm) does not pass through the anastomotic stricture. Cases of pinhole stricture in which a device for dilation or RIC cannot pass through are ineligible.

**Exclusion criteria**

(i) Active infection requiring systemic therapy.

(ii) Body temperature ≥38°C.

(iii) Pregnancy, possible pregnancy, within 28 days after delivery or breastfeeding.

(iv) Psychiatric disease.

(v) Patients requiring systemic steroid medication.

(vi) Patients requiring continuous anticoagulant or antiplatelet drug.

(vii) Poorly controlled hypertension.

(viii) History of unstable angina within 3 weeks or myocardial infarction within 6 months.

(ix) Positive HBs antigen.

(x) Positive HBs antibody and/or HBc antibody with HBV-DNA ≥2.1 log copies/ml.

**Randomization**

After confirming fulfillment of the first inclusion criteria, first registration is made using a web-based system at the JCOG Data Center. The second registration should be done within 7 days from the first registration, and it is carried out by telephone to the JCOG Data Center or using the web-based system. Patients are randomized to either arm A (EBD) or arm B (RIC) by a minimization method balancing the arms with institution, past history of receiving radiotherapy, duration between first endoscopic dilation to an anastomotic stricture and esophagectomy (90 days or less vs. 91 days or more).

**Quality control of RIC**

Thirty institutions among the GIESG of the JCOG participate in this trial. All participating endoscopists have agreed to the technical details for RIC. All procedures of RIC with steroid injection are carried out by endoscopists certified by the Study Chair. The minimum requirements for certification in this study are as follows:

(i) Ten or more experiences of ESD procedures for esophageal cancer and esophageal perforation of 10% or less.

(ii) At least one experience of RIC procedure without complication (the definition of a complication is the same as the endpoint of this study).

It is mandatory to take photographs and record movies of the RIC procedure in all patients randomized to the RIC arm. When perioperative complications are clearly observed in a specific institution or when it takes >60 min to finish all procedures, we pick up these cases in a semiannual monitoring report and the photographs and movies will be reviewed for quality control of the RIC procedure in the group meeting which is held twice a year.

With regard to EBD, we do not set specific rules about quality control of EBD procedure. However, when it takes >30 min to finish all procedures of EBD with steroid injection, we pick up these cases in the monitoring report and discuss them in the group meeting.

**Treatment methods**

**EBD or RIC with steroid injection**

As for EBD, there are no specific criteria regarding the balloon device. The diameter of the balloon is chosen based on the diameter of anastomotic stricture. As for RIC, use of an IT knife is recommended. RIC will be carried out as follows:

(i) The stricture area is incised radially by using an IT knife endoscopically.

(ii) The imaged line that connects the esophageal lumen on the oral side and the lumen on the anal side is assumed, and an incision is performed along this line.

(iii) The incision area is sliced off with an IT knife.

(iv) Whether an endoscope can pass through the dilated stricture is confirmed.

(v) A photograph of the dilated stricture is taken.

After EBD or RIC, steroid (triamcinolone acetonide) injection to the dilated anastomotic stricture is performed in all patients. The total
amount of injected triamcinolone is 40 mg/4 ml and an injection of 0.5–1.0 ml to each injection site is recommended.

**Endoscopic dilation to the anastomotic stricture after EBD or RIC with steroid injection**

After performing EBD or RIC with steroid injection as the initial treatment, dysphagia scores are evaluated at 2, 4, 8 and 24 weeks after the initial treatment. Eight weeks after the initial treatment, endoscopy will be planned. If a dysphagia score of >1 is observed, endoscopy is performed and EBD with steroid injection is given when an endoscope for routine examination (diameter: 9.6–10.4 mm) does not pass through the anastomosis. Patients are observed for 24 weeks after the initial treatment. EBD with steroid injection within 24 weeks after the initial treatment is regarded as protocol treatment.

**Follow-up**

Patients need to be followed up until 24 weeks after the initial treatment. Even if the protocol treatment is terminated, evaluation of dysphagia score is needed up to 24 weeks after the initial treatment.

**Study design and statistical analysis**

This randomized Phase II/III trial is designed to confirm the superiority of RIC with steroid injection compared with EBD with steroid injection in terms of restricture-free survival and number of dilations for 24 weeks after treatment. The Phase II part is incorporated because the safety and efficacy of RIC combined with steroid injection have not been reported.

In the Phase II part, the planned sample size is 60, which is half the number of the total sample size and is considered to be appropriate to assess the safety of EBD or RIC with steroid injection.

In the Phase III part, the primary analysis is to be carried out 6 months after accrual completion. The total sample size is calculated considering two primary endpoints. As for restricture-free survival, we assumed the proportion of re-stricture-free survival at 6-month to be 25% for EBD and expected a 25% increase in the proportion of re-stricture-free survival at 6-month for RIC. According to Schoenfeld and Richter’s method (20), the sample size was calculated as 60 patients per arm with a one-sided α level of 5%, power of 90% and a follow-up period of 6 months. As for the number of dilations for 24 weeks after treatment, the sample size was calculated according to the O’Brien and Castelloe method (21), as 54 patients per arm with a one-sided α level of 5% and power of 90%, assuming the distribution of dilation number per patient as follows: 25% of patients in arm A and 50% in arm B would receive endoscopic dilation zero times, 15% in both arms one time, 15% in arm A and 10% in arm B two times, 15% in arm A and 10% in arm B three times, 15% in arm A and 10% in arm B four times, 10% in arm A and 5% in arm B five times and 5% in arm A and 0% in arm B more than five times.

Assuming two calculated sample sizes based on each primary end-point and patients lost to follow-up, the total sample size was set at 130 patients. It is planned to have an expected accrual period of 3 years. All statistical analyses will be conducted at the JCOG Data Center.

**Interim analysis and monitoring**

We plan to conduct one interim analysis. The interim analysis for the primary endpoint in the Phase II part will be conducted after 30 patients in each arm have been enrolled (patient accrual in the Phase II part is completed) to determine whether we can proceed to the Phase III part. The Data and Safety Monitoring Committee (DSMC) of the JCOG will review the interim analysis reports independently from the group investigators and group statistician. The trial will be terminated when Grade 3/4 intraoperative hemorrhage, post-operative esophageal perforation, esophageal hemorrhage, pneumothorax, lung or mediastinum infection or other unexpected adverse reactions are observed in more than three patients in either arm.

In-house monitoring will be performed every 6 months by the JCOG Data Center to evaluate and improve study progress, data integrity and patient safety.

**Participating institutions (from north to south)**

Iwate Medical University Hospital, Iwate; Iwate Prefectural Central Hospital, Iwate; Yamagata Prefectural Central Hospital, Yamagata; Ibaraki Prefectural Central Hospital and Cancer Center, Ibaraki; Tochigi Cancer Center, Tochigi; National Cancer Center Hospital East, Chiba; Chiba Cancer Center, Chiba; National Cancer Center Hospital, Tokyo; Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo; Toranomon Hospital, Tokyo; NTT Medical Center, Tokyo; Kitasato University School of Medicine, Kanagawa; Yokohama City University Medical Center, Kanagawa; Niigata University Medical and Dental Hospital, Niigata; Toyama Prefectural Central Hospital, Toyama; Ishikawa Prefectural Central Hospital, Ishikawa; Saku Central Hospital, Nagano; Shizuoka Cancer Center, Shizuoka; Aichi Cancer Center Hospital, Aichi; Aichi Cancer Center Aichi Hospital, Aichi; Kyoto University Hospital, Kyoto; Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; Osaka Medical College, Osaka; Kobe University Graduate School of Medicine, Hyogo; Hyogo Cancer Center, Hyogo; Sano Hospital, Hyogo; Hiroshima City Hospital, Hiroshima; Hiroshima City Asa Hospital, Hiroshima; National Hospital Organization Shikoku Cancer Center, Ehime; Kochi Health Sciences Center, Kochi.

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**Conflict of interest statement**

None declared.

**References**


