

Clinical Trial Note

## A Phase II Trial of Combined Treatment of Endoscopic Mucosal Resection and Chemoradiotherapy for Clinical Stage I Esophageal Carcinoma: Japan Clinical Oncology Group Study JCOG0508

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Standard treatment for clinical stage I esophageal cancer with submucosal invasion (T1b) has been surgical resection. We conducted a Phase II trial to evaluate the efficacy and the safety of combined treatment of endoscopic mucosal resection (EMR) and chemoradiotherapy for clinical stage I (T1b) esophageal cancer. Patients diagnosed as having clinical stage I (T1b) esophageal cancer which is considered to be resectable by EMR are eligible. When pathological examination of the EMR specimen confirms T1b tumor with negative or positive resection margin, the patient undergoes chemoradiotherapy. The study continues until 82 patients with T1b tumor with negative resection margin are enrolled from 20 institutions. The primary endpoint is 3-year overall survival (OS) in pT1b cases with negative resection margin. The secondary endpoints are 3-year OS and progression-free survival in all eligible cases, OS in pT1a-MM cases with margin-negative, complications of EMR and adverse events of chemoradiotherapy. The data from this trial will be expected to provide a non-surgical treatment option to the patients with clinical stage I (T1b) esophageal cancer.

*Key words: superficial esophageal cancer – endoscopic mucosal resection – chemoradiotherapy*

### INTRODUCTION

According to the Japanese Classification of Esophageal Cancer by the Japan Esophageal Society, T1 esophageal tumors defined by the TNM system (6th edition) is further divided into T1a (mucosal) and T1b (submucosal) tumors by the Japanese Classification of Esophageal Cancer (1). Endoscopic mucosal resection (EMR) is usually indicated for T1a tumor, whereas the standard treatment for T1b tumors has been a surgical resection with adequate lymph node dissection in Japan because of the high incidence of lymph node metastasis (~40%) (2). However, surgical

resection often deteriorates patient's general condition. Some patients with clinical T1b esophageal cancer are over-treated by surgery with a result of pathological T1a tumor, because the accuracy of diagnosis of T1b esophageal cancer is not high.

Recent advance in techniques of EMR including endoscopic submucosal dissection (ESD) enables us to remove the clinical T1b tumor and gives us accurate diagnosis of depth of invasion. However, the patients with T1b are at risk of lymph node metastasis (3) and therefore EMR alone cannot be considered as curative.

Chemoradiotherapy is one of the effective modalities for both early and advanced esophageal tumors. Since chemoradiotherapy is less toxic than surgical resection, the usefulness has been tested in several clinical trials (4,5). In Japan,

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a Phase II trial (JCOG9708) was conducted to evaluate the efficacy and the safety of concurrent chemoradiotherapy using 5-fluorouracil (5-FU) plus cisplatin (CDDP) for T1 tumors (6). However, 22% of patients showed minor relapses that needed to be removed by endoscopic treatment. We have therefore conducted a pilot study of EMR followed by chemoradiotherapy and have reported promising results (7). Thus, the Japan Clinical Oncology Group initiated this multi-institutional Phase II trial (JCOG0508) to evaluate the efficacy and the safety of combined treatment of EMR and chemoradiotherapy for clinical stage I (cT1bN0) esophageal cancer.

The Protocol Review Committee of JCOG approved the protocol in October 2006 and the study was activated in December 2006.

## JCOG0508 PROTOCOL

### PURPOSE

The aim of this study is to evaluate the efficacy and the safety of combined treatment of EMR and chemoradiotherapy for clinical stage I (T1b) esophageal cancer.

### STUDY SETTING

The study is a multi-institutional (20 centers), single-arm Phase II trial.

### RESOURCES

This study is supported by the Grants-in-Aid for Cancer Research (17S-3, 17S-5, 20S-3, 20S-6) and Health and Labour Sciences Research Grant for Clinical Cancer Research (17-12) from the Ministry of Health, Labour and Welfare, Japan.

### ENDPOINTS

The primary endpoint is 3-year overall survival (OS) in pT1b cases with negative resection margin (comment 4). The secondary endpoints are 3-year OS and progression-free survival (PFS) in all eligible cases, OS in pT1a-MM (muscularis mucosa) cases with negative resection margin, complications of EMR and adverse events of chemoradiotherapy.

In this trial, resection margin is diagnosed from endoscopic findings immediately after mucosal resection for horizontal margin and from pathological findings for vertical margin. OS is defined as the time from registration to death from any cause, and it is censored at the last contact day for living patient. PFS is defined as the time from registration to either the first event of progression or death from any cause, and it is censored at the latest day when patient is alive without progression.

### INCLUSION CRITERIA

Patients are included in this trial if they meet all of the following criteria: (i) histologically proven squamous cell carcinoma of the esophagus by endoscopic biopsy, (ii) tumors located within the thoracic esophagus, (iii) depth of tumor invasion is diagnosed as T1b by endoscopy and endoscopic ultrasonography, (iv) the number of multiple intra-esophageal tumors is less than three, and the depths of invasion of them are diagnosed as cT1a-EP (carcinoma *in situ*) or cT1a-LPM (tumor invades lamina propria mucosa), (v) clinically node-negative (cN0) and no metastasis to other organs (cM0), (vi) size of main tumor is  $\leq 5$  cm, and circularity of esophageal lumen is less than three-fourths, (vii) no ulcerative lesion in the tumors, (viii) no intra-esophageal metastasis, (ix) no prior treatment of chemotherapy or radiation therapy against any other malignancies, except for previous curative EMR for pT1 esophageal cancer, (x) aged between 20 and 75 years old, (xi) performance status of 0 or 1, (xii) sufficient organ functions and (xiii) written informed consent.

### EXCLUSION CRITERIA

Patients are excluded if they meet any of the following criteria: (i) iodine allergy, (ii) unable to discontinue anticoagulant or antiplatelet medications, (iii) synchronous or metachronous (within 5 years) malignancy other than carcinoma *in situ*, (iv) pregnant or breast-feeding women, (v) severe mental disease, (vi) systemic administration of corticosteroids, (vii) HBs antigen positive, (viii) active bacterial or fungus infection, (ix) concurrent unstable angina or myocardial infarction within 3 months before registration, (x) unstable hypertension, (xi) diabetes mellitus, uncontrolled or controlled with insulin, or (xii) interstitial pneumonia, lung fibrosis or severe emphysema.

### REGISTRATION

After confirming the inclusion/exclusion criteria by telephoning or faxing the JCOG Data Center, the patients are registered into this JCOG0508 trial.

### QUALITY CONTROL OF EMR

Twenty institutions among the Gastrointestinal Oncology Study Group of the JCOG participate in this trial. All participating physicians have agreed to the technical details for EMR. For quality control of EMR technique and endoscopic diagnosis, we perform central review of the photographs in all patients at the semi-annual investigators meeting. Regarding an ESD procedure, we permit it only for expert physicians who have significant experiences in ESD and EMR, and they are registered by the primary investigator (M.M.). The minimum request for ESD permission is the experience of EMR  $\geq 50$  and ESD  $\geq 10$  for esophageal

carcinoma, ESD  $\geq 50$  for gastric cancer and perforation rate  $\leq 2\%$  in total.

#### TREATMENT METHODS

##### ENDOSCOPIC MUCOSAL RESECTION

EMR is performed against esophageal tumors within 30 days from registration. The technical methods of EMR approved in this trial are a two-channel method, a cap method or an esophageal endoscopic mucosal resection-tube method (8). Only the registered physicians are allowed to perform ESD in this trial. After EMR, it should be confirmed endoscopically that no iodine-unstained area is left. Physicians need to take pictures before and after EMR and submit them to the primary investigator for quality control of EMR technique and endoscopic diagnosis.

##### CHEMORADIOTHERAPY

In cases of pT1a tumor with negative resection margin and no vascular invasion, no additional treatment after EMR is given. In other cases, chemoradiotherapy was started at 29–70 days after EMR. The chemotherapy regimen is continuous 5-FU (700 mg/m<sup>2</sup>/day, days 1–4 and 29–32) and CDDP (70 mg/m<sup>2</sup>/day, days 1 and 29). The dose of radiotherapy is 41.4 Gy/23 Fr/5 weeks (5 days/week) for cases with negative resection margin and 50.4 Gy/28 Fr/5 weeks (5 days/week) with boost on the primary site for the case with positive resection margin, respectively.

##### FOLLOW-UP

Patients are followed with blood tests, upper gastrointestinal endoscopy and computed tomography at least every 4 months for 3 years.

##### STUDY DESIGN AND STATISTICAL METHODS

This trial determines the efficacy and the safety of combined treatment of EMR and chemoradiotherapy for cT1b esophageal cancer in terms of 3-year OS. Additionally, 3-year OS in all eligible patients are evaluated as the most important secondary endpoint. The sample size is 82 for pT1b cases with negative resection margin with the power of 90%. In case this hypothesis rejected, the secondary hypothesis for all eligible patients can be tested using hierarchical method keeping trial-wise  $\alpha$  error nominal level, one-sided 5%, with the power of 80%. To test the hypothesis, 3-year OS estimated by Kaplan–Meier method and its confidence interval by Greenwood's formula is used. The total number of registered patients is estimated as 137, because the proportion of pT1b cases with margin-negative among all eligible patients is predicted as  $\sim 60\%$ .

This study was registered with UMIN-CTR [www.umin.ac.jp/ctr/], identification number UMIN000000553.

#### INTERIM ANALYSIS AND MONITORING

Interim analysis is not planned. If the number of cases with treatment-related death, severe (Grade 4) bleeding or severe (Grade 4) perforation reaches seven, the registration will be suspended unless the JCOG Data and Safety Monitoring Committee approves to continue this trial. The JCOG Data Center is responsible for data management, central monitoring and statistical analysis. This center also provides semi-annual monitoring reports, each of which is submitted to and reviewed by the JCOG Data and Safety Monitoring Committee on demand of the JCOG Data Center. None of physicians administering the interventions are involved in the data analysis. For quality assurance, site-visit audits, not for a specific study basis but for the study group basis, are done by the JCOG Audit Committee.

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#### Conflict of interest statement

None declared.

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**Appendix**

The initially participating hospitals are as follows: Iwate Prefectural Central Hospital, Ibaragi Prefectural Central Hospital, Tochigi Cancer Center Hospital, National Cancer Center Hospital East, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Showa University Hospital, Cancer

Institute Ariake Hospital, Kitasato University East Hospital, Kanagawa Cancer Center Hospital, Ishikawa Prefectural Central Hospital, Saku Central Hospital, Shizuoka Cancer Center Hospital, Aichi Cancer Center Central Hospital, Kyoto University Hospital, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka City Medical Center, and Osaka Medical College Hospital.