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Clinical Trial Notes

A Phase II Clinical Trial of Endoscopic Submucosal Dissection for Early Gastric Cancer of Undifferentiated Type: Japan Clinical Oncology Group Study JCOG1009/1010

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A Phase II clinical trial has been initiated to evaluate the efficacy and safety of endoscopic submucosal dissection for intramucosal (cT1a) gastric cancer of undifferentiated type. Patients with cT1a gastric cancer with undifferentiated-type adenocarcinoma are eligible for the study. The tumor size should be 2 cm or less without ulceration. The study will enroll a total of 325 patients from 51 institutions over a 4-year period. The primary endpoint is proportion of 5-year overall survival (% 5-year overall survival) in patients with undifferentiated dominant type. The secondary endpoints are overall survival, relapse-free survival, distant metastasis-free survival, % 5-year overall survival without either recurrence or gastrectomy, % en-bloc resection with endoscopic submucosal dissection, % pathological curative resection with endoscopic submucosal dissection, % 5-year overall survival in patients with differentiated dominant type, % 5-year overall survival in patients with pathologically curative resection with endoscopic submucosal dissection and adverse events. This trial was registered at the UMIN Clinical Trials Registry as UMIN000004995.

Key words: clinical trial-trial design – clinical trials – endoscopy-upper GI

INTRODUCTION

Gastrectomy with lymph node dissection has been the standard treatment in patients with early gastric cancer (EGC) in Japan, because complete cure can almost always be achieved (1). On the other hand, endoscopic resection (ER) is an attractive alternative for some EGC because it is a minimally invasive, stomach-conserving procedure and postoperative quality of life is better.

The indications for ER are limited to EGC without lymph node metastasis because the treatment involves only local resection without lymph node dissection. As per the Japanese Gastric Cancer Treatment Guidelines 2010 (ver.3) set forth by the Japan Gastric Cancer Association, the indication for ER is

limited to intramucosal (cT1a) lesions of differentiated (intestinal) type 2 cm or less in diameter, based on the potential for lymph node metastasis and technique for en-bloc resection.

A large retrospective study of surgically resected cases showed that some cT1a (i.e. mucosal cancer without ulceration (UL) regardless of its size and intramucosal cancer with UL 3 cm or less) demonstrated no lymph node metastasis (2). Moreover, recent technical advances in ER, including endoscopic submucosal dissection (ESD) (3), have enabled en-bloc resection of cT1a tumors larger than 2 cm (4). Thus, it is speculated that ER using ESD techniques may cure some patients with differentiated type of EGC beyond the indications described in the current practice guidelines. A multi-institutional clinical trial, by Japan Clinical Oncology Group (JCOG0607), is currently in progress to examine these indications, as previously reported (5).

With regard to EGC of undifferentiated (diffuse) type, a consensus could not be reached as to which lesions present a negligible risk of lymph node metastasis in the above-mentioned retrospective analysis because of the small sample size (2). Hirasawa et al. (6) recently reviewed additional surgical data 9 years after the initial publication. They concluded that intramucosal EGC of undifferentiated that are 2 cm or less in size, without lymphovascular invasion and UL, presented a negligible risk of lymph node metastasis. In addition, Yamamoto et al. (7) reported excellent results with regard to ESD for undifferentiated-type EGC, with a high proportion of curative resection. From the results of these two reports, we speculated that ER using ESD techniques would be an appropriate indication for certain EGC of undifferentiated type. A multi-institutional Phase II trial (JCOG1009/1010) was therefore initiated to evaluate the efficacy and safety of ESD for EGC of undifferentiated type beyond currently accepted indications (Fig. 1). JCOG1009/1010 is a collaborative study between the two JCOG study subgroups: JCOG1009 is a part of the study by the Gastrointestinal Endoscopy Study Group (GIESG) and JCOG1010 is a part of the study by Stomach Cancer Study Group (SCSG) of the JCOG. JCOG1009/1010 has one common protocol and one primary analysis.

The JCOG Protocol Review Committee approved the protocol in December 2010. The study was registered in the UMIN Clinical Trial Registry [www.umin.ac.jp/ctr/] as UMIN000004995, and activated in February 2011.

JCOG1009/1010 PROTOCOL

Purpose

The aim of this study is to evaluate the efficacy and safety of ESD for intramucosal gastric cancer of undifferentiated type, clinically diagnosed as intramucosal cancer 2 cm or less in size without ulceration.

Study Setting

Multi-institutional (51 centers), single-arm, Phase II trial.

Resources

This study is supported by the Grants-in-Aid for Cancer Research (20S-3 and 20S-6), the National Cancer Center Research and Development Fund (23-A-16 and 23-A-19) and Health and Labour Sciences Research Grant for Clinical Cancer Research (22−021) from the Ministry of Health, Labour and Welfare, Japan.

Endpoints

The primary endpoint is proportion of 5-year overall survival (% 5-year OS) in patients with undifferentiated dominant-type EGC diagnosed in the ESD specimen (Fig. 1). The secondary endpoints are OS, relapse-free survival (RFS), distant metastasis-free survival, % 5-year survival without either recurrence or gastrectomy, % en-bloc resection with ESD, % pathologically curative resection with ESD, % 5-year OS in patients with differentiated dominant-type EGC diagnosed in the ESD specimen, % 5-year OS in patients with pathologically curative resection with ESD and adverse events.

In this trial, OS is defined as the time from registration to death from any cause, and it is censored at the last contact day for a living patient. RFS is defined as the time from registration to either the first event of recurrence or death from any cause, and it is censored at the last day when the patient is alive without recurrence. Adverse events are evaluated according to Common Terminology Criteria for Adverse Events version 4.0—JCOG. The criteria for pathologically curative resection are described in 'Decision criteria after ESD' section.

Inclusion Criteria

Patients are eligible for inclusion in the study if they meet all of the following criteria: (i) histologically proven components of undifferentiated (diffuse)-type adenocarcinoma (por or sig) of the stomach in biopsy specimen; (ii) confirmation of the horizontal margin by cancer-free endoscopic biopsy around the lesion, which should be examined at each participating institution; (iii) non-recurrent single tumor; (iv) clinical T1a (intramucosal); (v) tumor size 2 cm or less; (vi) absence of ulcer findings endoscopically; (vii) low likelihood for luminal stenosis after ESD; (viii) clinical N0/M0 by abdominal CT scan; (ix) age 20−80 years old; (x) performance status (ECOG) of 0 or 1; (xi) no prior gastrectomy and no reconstructive surgery involving the stomach for esophageal cancer; (xii) no prior chemotherapy (including hormone therapy) or radiation therapy for any other malignancies; (xiii) sufficient organ function and (xiv) written informed consent.

Exclusion Criteria

Patients are excluded from the study if they meet any of the following criteria: (i) simultaneous or metachronous (within

	cT1a (mucosa)			
	UL (−)		UL (+)	
	≤20 mm	>20 mm	≤30 mm	>30 mm
Differentiated (intestinal)	Absolute indication by the guideline	Expanded indication, being evaluated in JCOG0607	expanded indication being evaluated in JCOG0607	No indication, requiring surgery
Undifferentiated (diffuse)	No indication, being evaluated in this study, JCOG1009/1010	No indication, requiring surgery	No indication, requiring surgery	No indication, requiring surgery

Figure 1. Indications for endoscopic resection of early gastric cancer.

5 years) multiple cancers, except intramucosal tumor curable with local therapy; (ii) infectious disease requiring systemic therapy; (iii) body temperature higher than 38°C; (iv) pregnant or breast-feeding woman; (v) psychosis; (vi) use of systemic steroids; (vii) history of myocardial infarction within 6 months or unstable angina pectoris within 3 weeks; (viii) uncontrolled hypertension; (ix) severe respiratory disease requiring continuous oxygen therapy; (x) inability to hold anticoagulant or antiplatelet medications and (xi) uncontrolled diabetes mellitus or administration of insulin.

Registration

Patients are registered into the JCOG1009/1010 trial after confirming the inclusion/exclusion criteria by telephone or fax to the JCOG Data Center. Online website registration is also available.

Quality Control of ESD

Thirty institutions among the GIESG and 21 institutions among the SCSG of the JCOG are participating in this trial (Table 1). All participating endoscopists have agreed to the technical details for ESD. To control the quality of the ESD technique and endoscopic diagnosis, central review of photographs and videotapes in arbitrarily selected patients will be performed at the semi-annual investigators' meeting. All ESD procedures are done or directly supervised endoscopists certified by study chair. The minimum criterion for certification in this study is having experience with 50 or more ESD for gastric cancer.

Treatment Methods

Endoscopic Submucosal Dissection

ESD of EGC is performed within 30 days after patient registration. Tumors should be resected en-bloc with ESD, and ESD should be performed by certified endoscopists or other staff members under the supervision of certified endoscopists. There are no specific criteria regarding devices used for ESD.

Decision Criteria after ESD

After ESD, patients are categorized into two groups: undifferentiated type group and differentiated-type group, according to the dominant histopathology diagnosed in the resected specimens. In both groups, ESD is deemed 'non-curative' if any of the following criteria is met in the histological diagnosis of resected specimens;

(A) undifferentiated type group:
  (i) pT1b (submucosa, SM),
  (ii) with UL,
  (iii) size of tumor >2 cm;
(B) differentiated type group:
  (i) pT1a (M) with UL and size of tumor ≥3 cm,
  (ii) pT1b (SM1; tumor invasion is within 0.5 mm beyond the muscularis mucosae) with a component of undifferentiated type adenocarcinoma in the most advanced area,
  (iii) pT1b (SM1) and size of tumor 3 cm or more,
  (iv) depth of tumor invasion is pT1b (SM2, tumor invasion is 0.5 mm or deeper beyond the muscularis mucosae) or more,
  (v) pT1a (M) without UL and size of undifferentiated type histology component 2 cm or more;
(C) both groups:
  (i) vascular or lymphatic invasion present,
  (ii) histological vertical margin positive or non-evaluable,
  (iii) histological horizontal margin positive or non-evaluable,
  (iv) tumors not treated in en-bloc resection,
  (v) intratumor resection found pathologically,
  (vi) presence of component of muc (mucinous adenocarcinoma).

'Non-curative' cases must undergo gastrectomy according to the Japanese Gastric Cancer Treatment Guidelines.

ESD is deemed 'curative' if none of the above criteria are met. 'Curative' cases receive no additional treatment after ESD.

Table 1. Participating institutions

GIESG (30 institutions)

1. Iwate Prefectural Central Hospital, Iwate
2. Iwate Medical University Hospital, Iwate
3. Yamagata Prefectural Central Hospital, Yamagata
4. Ibaraki Prefectural Central Hospital, Ibaraki
5. Tochigi Cancer Center, Tochigi
6. National Cancer Center Hospital East, Chiba
7. Asahi Hospital, Chiba
8. Chiba Cancer Center, Chiba
9. National Cancer Center Hospital, Tokyo
10. Showa University Hospital, Tokyo
11. Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo
12. Toranomon Hospital, Tokyo
13. Kanagawa Cancer Center, Kanagawa
14. Yokohama Municipal Citizen's Hospital, Kanagawa
15. Kitasato University East Hospital, Kanagawa
16. Yokohama City University Medical Center, Kanagawa
17. Ishikawa Prefectural Central Hospital, Ishikawa
18. Saku Central Hospital, Nagano
19. Shizuoka Cancer Center Hospital, Shizuoka
20. Aichi Cancer Center, Aichi
21. Aichi Cancer Center Aichi Hospital, Aichi
22. Kyoto University Graduate School of Medicine, Kyoto
23. Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka
24. Osaka City General Hospital, Osaka
25. Kobe University Hospital, Hyogo
26. Hyogo Cancer Center, Hyogo
27. Shikoku Cancer Center, Ehime
28. Kochi Health Sciences Center, Kochi
29. Sano Hospital, Hyogo
30. Hiroshima City Hospital, Hiroshima

SCSG (21 institutions)

1. Sendai Medical Center
2. Miyagi Cancer Center
3. Tokyo Metropolitan Bokutoh Hospital
4. Niigata Cancer Center Hospital
5. Tsubame Rosai Hospital
6. Toyama Prefectural Central Hospital
7. Gifu Municipal Hospital
8. Shizuoka General Hospital
9. Kyoto Medical Center
10. Japanese Red Cross Kyoto Daini Hospital
11. Osaka University
12. Kinki University
13. Osaka National Hospital
14. Osaka Medical College
15. Sakai Municipal Hospital
16. Hyogo College of Medicine, Hyogo
17. Itami City Hospital, Hyogo
18. Tenri Hospital, Nara
19. Wakayama Medical University
20. Hiroshima City Asa Hospital, Hiroshima
21. Oita University Hospital, Oita

Follow-up

All enrolled patients are followed for at least 5 years. Follow-up includes serum tumor markers (CEA and CA19-9), upper GI endoscopy, chest X-ray (or CT) and abdominal CT at least every 6 months for the first 3 years, and then annually.

Central Pathology Review

To reduce the institutional variation in pathological diagnosis, central pathology review of all resected specimens by ESD will be performed. Prior to initiation of this study, pathologists from participating institutions attended the investigators' meeting to share the consensus in pathological assessment for the ESD specimens.

Study Design and Statistical Methods

This trial is designed as a confirmatory trial to determine the efficacy and safety of ESD for cT1a undifferentiated-type early gastric cancer in terms of 5-year OS. Primary analysis will be carried out for the patients with undifferentiated dominant-type diagnosed in ESD specimen (Fig. 2). The sample size for undifferentiated type is planned to be 193 (anticipated total number of registered patients, 276) with 5 years of follow-up and an accrual period of 4 years. This sample size provided 70% power under the hypothesis of primary endpoint as the expected value of 93.2% and threshold value of 88.2% using one-sided testing at 5% significance level. However, because the accrual rate was higher than expected, the sample size was re-evaluated. By the protocol revision, the final sample size based on registered patients was 325 (259 with undifferentiated type), provided 80% power under the hypothesis of primary endpoint as the expected value 94.7% and threshold value of 89.7% using one-sided alpha of 0.025. To test the hypothesis, 5-year OS estimated by the Kaplan–Meier method and its confidence interval based on Greenwood's formula are used.

Interim Analysis and Monitoring

Interim analysis is not planned. If the number of cases with treatment-related death, severe (grade 3 or 4) bleeding or

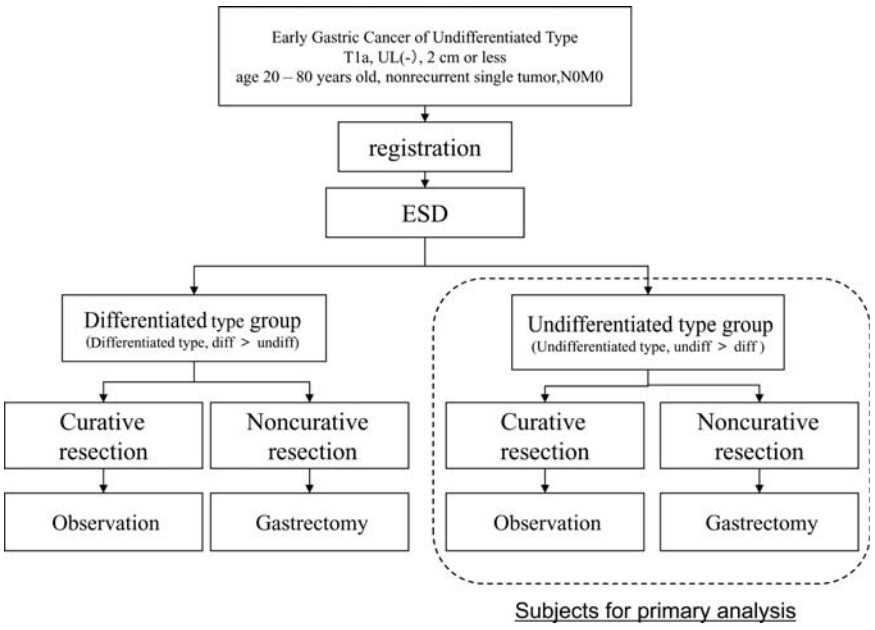

Figure 2. Study schema.

severe (grade 3 or 4) perforation reaches 2, 8 or 19, respectively, the registration will be suspended unless the JCOG Data and Safety Monitoring Committee approves continuation of the trial. The JCOG Data Center is responsible for data management, central monitoring and statistical analysis. JCOG Data Center also provides semi-annual monitoring reports, submitted to and reviewed by the JCOG Data and Safety Monitoring Committee. None of the physicians performing the interventions will be involved in the data analysis. For quality assurance, site-visit audits, not for a specific study basis but for the study group basis, will be performed by the JCOG Audit Committee.

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Conflict of interest statement

None declared.

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