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Protocol for a single-arm confirmatory trial of adjuvant chemoradiation for patients with high-risk rectal submucosal invasive cancer after local resection: Japan Clinical Oncology Group Study JCOG1612 (RESCUE study)

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ABSTRACT

Introduction Intestinal resection with lymph node dissection is the current standard treatment for high-risk lower rectal submucosal invasive cancer after local resection; however, surgery affects patients' quality of life due to stoma placement or impaired anal sphincter function. A recent study demonstrated that adjuvant chemoradiation yields promising results.

Methods and analysis This study aims to confirm the non-inferiority of adjuvant chemoradiation, consisting of capecitabine and concurrent radiotherapy (45 Gy in 25 fractions), measured by 5-year relapse-free survival (RFS), over standard surgery in patients with high-risk lower rectal submucosal invasive cancer after local resection. The primary endpoint is 5 year RFS. The secondary endpoints are 10 years RFS, 5-year and 10-year overall survival, 5-year and 10-year local RFS, 5-year and 10-year proportion of anus-preservation without stoma, Wexner score, low anterior resection syndrome score, adverse events and serious adverse events. During the 5-year trial period, 210 patients will be accrued from 65 Japanese institutions.

Ethics and dissemination The National Cancer Center Hospital East Certified Review Board approved this study protocol in October 2018. The study is conducted in accordance with the precepts established in the Declaration of Helsinki and Clinical Trials Act. Written informed consent will be obtained from all eligible patients prior to registration. The primary results of this study will be published in an English article. In addition, the main results will be published on the websites of Japan Clinical Oncology Group (www.jcog.jp) and jRCT (https://jrct.niph.go.jp/). As to data curation, it has not been prepared yet.

Trial registration number jRCT1031180076

Strengths and limitations of this study

- ► This is the first prospective trial to investigate the non-inferiority of adjuvant chemoradiation for high-risk lower rectal submucosal invasive cancer after local resection.
- ► The trial could support this less invasive treatment as a new standard of care with anus preservation without stoma and anal function.
- ► Selection bias cannot be excluded because this is a non-randomised study; given the comparison with historical data of surgery, there is a low possibility of overestimating 5-year relapse-free survival by influence of selection bias due to the excellent prognosis of this study population.

INTRODUCTION

With recent advances in surgery and endoscopic treatment approaches, most patients with early-stage colorectal cancer initially undergo local resection, such as endoscopic resection and local excision. After local resection, some patients are determined to be at high risk for lymph node metastasis based on the presence of one or more of the following pathological findings: (1) depth of submucosal (SM) invasion≥1000 µm, (2) lymphovascular invasion, (3) poorly differentiated adenocarcinoma, signet-ring cell carcinoma or mucinous carcinoma and (4) grade 2/3 budding at the site of the deepest invasion. For patients with high-risk factors, surgical intestinal resection with lymph node dissection is still considered standard treatment.[1]

The proportion of lymph node metastasis is only 10%–15% in patients with high-risk early colorectal cancer after local resection, who have a good prognosis.[2–4] While

Ikematsu *et al* reported that 5-year disease-free survival was 96.4% after surgical intestinal resection with lymph node dissection in patients with high-risk lower rectal SM invasive cancer,[4] the surgical approach impacts the quality of life of the patients due to stoma placement and weakened anal sphincter function.[5–9] Between 2007 and 2011, the Colorectal Cancer Study Group of the Japan Clinical Oncology Group (JCOG) conducted a questionnaire survey across 42 participating institutions to survey the extent of shortcomings of the intestinal resection with lymph node dissection as initial treatment or additional treatment approach after local resection for rectal cancer. The proportion of patients with permanent stoma was 4.2%, whereas the proportion of patients in whom anus could not be preserved due to various causes, such as surgical complication and relapse, was 7.1%. In addition, the prognosis is worse in patients with high-risk lower rectal SM invasive cancer who do not undergo additional treatment. Given that the 5-year disease-free survival in this patient population is 78.0%, as reported by Ikematsu *et al*,[4] less invasive treatment approaches are needed.

Some studies evaluated additional chemoradiation (CRT) as a less invasive treatment option. A phase II trial reported by Sasaki *et al* evaluated CRT consisting of 5-week intravenous injection of 5-fluorouracil (5-FU) (250 mg/m^2/day) and concurrent radiotherapy (45 Gy in 25 fractions) in patients with high-risk pT1 (depth of SM invasion≥1000 µm and/or lymphovascular invasion) or pT2 lower rectal cancer after local excision.[9] The proportion of the protocol treatment completion was 86% (49/57) without serious adverse events, persistent treatment-related complications or anal dysfunction after local excision. The quality of life after CRT was, therefore, comparable to that before CRT. The 5-year disease-free survival was 94.2% in 53 patients with pT1 lesions and 75% in 4 patients with pT2 lesions. Although the results of this phase II trial were promising, the sample size was not large enough to establish adjuvant CRT as a treatment option. In addition, previous studies reported that capecitabine was non-inferior to 5-FU in neoadjuvant CRT regimens for patients with locally advanced rectal cancer, with less toxicity.[10 11]

Based on these results, we hypothesise that adjuvant CRT consisting of capecitabine and radiotherapy is an option or a new standard treatment for patients with high-risk lower rectal SM invasive cancer after local resection. This single-arm confirmatory trial (JCOG 1612) was therefore initiated to evaluate the efficacy and safety of adjuvant CRT for patients with high-risk lower rectal SM invasive cancer after local resection. JCOG 1612 is an intersubgroup study between two JCOG study groups: the Gastrointestinal Endoscopy Study Group and the Colorectal Cancer Study Group.

The JCOG Protocol Review Committee approved the study protocol in September 2018.

METHODS AND ANALYSIS

Study design and setting

JCOG1612 (RESCUE study) is designed as a multi-institutional, single-arm, confirmatory trial to confirm the non-inferiority of adjuvant CRT in patients with high-risk lower rectal SM invasive cancer after local resection.

The primary endpoint is 5-year relapse-free survival (RFS) in all registered patients. The secondary endpoints are 10-year RFS, 5-year and 10-year overall survival (OS), 5-year and 10-year local RFS (LRFS), and 5-year and 10-year proportion of anus-preservation without stoma, Wexner score, low anterior resection syndrome (LARS) score, adverse events and severe adverse events.

In this trial, OS is defined as the time from registration to death from any cause and censored at the last contact day for a living patient. RFS is defined as the time from registration to either the first event of relapse or death from any cause and censored at the last contact day for a living patient. LRFS is defined as the time from registration to either the first event of local relapse or death from any cause and censored at the last contact day for a living patient. Wexner score is a scoring tool aimed to assess the frequency and variety of incontinence,[12] and LARS score is a symptom-based scoring tool for bowel dysfunction after low anterior resection for lower rectal cancer, that correlates with quality of life.[13]

Eligibility criteria

Inclusion criteria

The inclusion criteria of this study are as follows:

1. Primary tumour located at lower rectum and upper border of the primary tumour located at the anal side of the middle Houston valve based on endoscopic findings before local resection. Local resection types include endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), transanal local resection, transanal endoscopic microsurgery (TEM) and minimal invasive transanal surgery (MITAS).
2. Within 12 weeks after local resection.
3. Complete en bloc resection performed by local resection with either (i) or (ii) as the pathological diagnosis:
   i. Horizontal margin-negative (HM0) and vertical margin-negative (VM0) after endoscopic resection (EMR or ESD).
   ii. Proximal margin-negative (PM0), distal margin-negative (DM0) and radial margin-negative (RM0) after surgical local resection (transanal local resection, TEM or MITAS).
4. Pathology stage T1 and adenocarcinoma as defined by the eighth edition of the Japanese Classification of Colorectal Carcinoma and fulfilling either of the following conditions:
   i. Poorly differentiated adenocarcinoma or mucinous adenocarcinoma, or signet-ring cell carcinoma.
   ii. Pathological T1b.

iii. Lymphatic invasion or venous invasion (confirmed using immunostaining).
iv. Budding grade of 2–3.
5. No exposure of ulcer bed, with evidence of covering with regenerative epithelium at the primary site after local resection confirmed endoscopically.
6. No lymph node or distant metastasis confirmed by chest, abdomen and pelvis-CT.
7. Age at registration between 20 and 75 years.
8. Eastern Cooperative Oncology Group performance status of 0 or 1.
9. Sufficient oral intake.
10. No prior rectal resection (excluding local resection) or pelvic irradiation for any malignancies.
11. No hereditary bowel disease (familial adenomatous polyposis or Lynch syndrome) or inflammatory bowel disease (ulcerative colitis or Crohn's disease).
12. Sufficient organ functions based on the following criteria:
i. White cell count≥3.0 x 10^9/L.
ii. Haemoglobin≥90 g/L.
iii. Platelet count≥100 x 10^9/L.
iv. Total bilirubin≤2.0 mg/dL.
v. Aspartate aminotransferase≤100 U/L.
vi. Alanine aminotransferase≤100 U/L.
vii. Creatinine≤1.5 mg/dL.
13. Explanation provided to the patient by the surgeons, that total mesorectal excision with D2 lymph dissection is standard therapy;
14. Written informed consent is obtained.

Exclusion criteria

Patient meeting any of the following criteria are excluded:
1. Synchronous or metachronous (within 5 years) malignancies except cancers with 5 years relative survival rates of 95% or more such as carcinoma in situ, intramucosal tumour or early-stage cancer.
2. Infections requiring systemic treatment.
3. Body temperature >38°C at registration.
4. Female patients who are pregnant, within 28 days of postparturition or breast feeding.
5. Severe psychiatric diseases.
6. Requirement for continuous systemic corticosteroid or immunosuppressant treatment.
7. Uncontrolled diabetes mellitus.
8. Unstable angina pectoris (angina developed, or attack worsened within the previous 3 weeks) or myocardial infarction within the previous 6 months.
9. Severe interstitial pneumonia, pulmonary fibrosis or severe emphysema.
10. Requirement for phenytoin or warfarin potassium.

Treatment

All registered patients receive chemotherapy with capecitabine (days 1–5, 8–12, 15–19, 22–26, and 29–33; 1800–3000 mg/day) in combination with radiotherapy (45 Gy in 25 fractions) for primary tumour bed and mesorectum after local resection. Endoscopic clipping before radiotherapy is recommended if CT for positioning does not specify the primary site, because endoscopy can detect the scar at the primary tumour site more accurately than MRI.

Follow-up

All registered patients are followed for at least 10 years after enrolment. Enhanced CT of the chest, abdomen and pelvis, colonoscopy and physical examination are performed every 6 months for the first 3 years after the termination of protocol treatment, and yearly thereafter for the next 7 years.

Patient and public involvement

Patients and the public were not involved in the development and the design of this study. Patients can find out the details of this study on the Japan Registry of Clinical Trial website. The final results will be disseminated to the public on the same website.

STATISTICAL CONSIDERATIONS

Sample size calculation and statistical analysis

This trial is designed as a single-arm trial to confirm the non-inferiority of adjuvant CRT in patients with high-risk lower rectal SM invasive cancer after local resection by assessing the primary outcome of 5 years RFS. The sample size is set at 210 with the expected value of 95%, threshold value of 90%, one-sided alpha of 5% and power of 80%. The difference of the expected and threshold value can be regarded as the non-inferiority margin of 5% to the historical control. The accrual period is 4 years, and the follow-up period is 10 years.

At 5 years after the accrual completion, primary analysis will be conducted. Kaplan-Meier method will be used to estimate the 5 years RFS and the CI will be calculated by Greenwood's formula. If the lower limit of the 90% CI exceeds the threshold value of 90%, non-inferiority to surgical results is confirmed and adjuvant CRT with capecitabine will be an option for standard of care. At 10 years after the accrual completion, in addition, if the 10-year proportion of anus-preservation without stoma is higher than 90% and 10 years RFS is not much lower than 90%, the standard of care will be replaced by adjuvant CRT. Primary analysis will be performed for all registered patients.

Patient registration and data entry

After confirming eligibility, registration with the JCOG Data Centre is performed by a web-based system.

Interim analysis and monitoring

Interim analysis is not planned because few events occur until the time of 3 years follow-up due to the excellent prognosis of this study population. If the number of treatment-related deaths reaches three, the registration will be suspended unless the JCOG Data and Safety Monitoring Committee approve the continuation of the trial.

The JCOG Data Centre and the study coordinator will conduct central monitoring and will issue a monitoring report every 6 months to evaluate study progress and improve data integrity and patient safety. For quality assurance, site visit audits will be performed by the JCOG Audit Committee.

ETHICS AND DISSEMINATION

Ethics approval and consent for participation

The participating institutions are as follows: Sapporo-Kosei General Hospital, Iwate Medical University, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Fukushima Medical University Hospital, Ibaraki Prefectural Central Hospital & Cancer Center, Tochigi Cancer Center, Gunma Prefectural Cancer Center, National Defense Medical College, Saitama Cancer Center, Saitama Medical Center Jichi Medical School, Saitama Medical University International Medical Center, Saitama Medical Center Saitama Medical University, National Cancer Center Hospital East, Chiba Cancer Center, National Cancer Center Hospital, Kyorin University Faculty of Medicine, Tokyo Medical University Hospital, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Keio University Hospital, Showa University School of Medicine, Tokyo Medical and Dental University Hospital, Toho University Ohashi Medical Center, Toho University Omori Medical Center, NTT Medical Center Tokyo, Kanagawa Cancer Center, Yokohama Municipal Citizen's Hospital, Kitasato University School of Medicine, Hiratsuka City Hospital, Niigata Cancer Center Hospital, Niigata University Medical and Dental Hospital, Toyama Prefectural Central Hospital, Ishikawa Prefectural Central Hospital, Gifu University School of Medicine, Shizuoka General Hospital, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Fujita Health University, Aichi Medical University, Kyoto University Hospital, National Hospital Organization Kyoto Medical Center, Osaka University Graduate School of Medicine, Osaka Redcross Hospital, Osaka International Cancer Institute, Osaka National Hospital, Osaka General Medical Center, Osaka City General Hospital, Osaka Medical College, Sakai City Medical Center, Suita Municipal Hospital, Kansai Rosai Hospital, Hyogo College of Medicine, Hyogo Cancer Center, Shimane University Faculty of Medicine, Kurashiki Central Hospital, Okayama Saiseikai General Hospital, Hiroshima University Hospital, Hiroshima City Hospital, Hiroshima Prefectural Hospital, Hiroshima City Asa Citizens Hospital, National Hospital Organization Shikoku Cancer Center, Kochi Health Sciences Center, Kurume University School of Medicine, Kumamoto University Medical School, Oita University Faculty of Medicine. These institutions were almost all aligned with JGES guidelines for colorectal endoscopic SM dissection/EMR.

The National Cancer Center Hospital East Certified Review Board approved this study protocol in October 2018. The study is conducted in accordance with the precepts established in the Declaration of Helsinki and Clinical Trials Act.

All patients will receive information for decision making to participate this trial. Consent to publication includes the general consent form, and each participant's data will be handled anonymously. All participants' information will be stored in the JCOG Data Center.

Dissemination

The primary results of this study will be published in an English article. In addition, the main results will be published on the websites of JCOG (www.jcog.jp) and jRCT (https://jrct.niph.go.jp/). As to data curation, it has not been prepared yet.

Individual participant data that underlie the results reported in this article will not be shared because the follow-up of the patients will continue until January 2033. After the publication, using data as of January 2033, individual participant data that underlie the results, after deidentification, will be shared if investigators whose proposed use of the data will be approved by the investigators from the Gastrointestinal Endoscopy Study Group and the Colorectal Cancer Study Group of JCOG identified for this purpose. Proposals should be directed to hikemats@east.ncc.go.jp. The date will be available for achieving aims in the approved proposal.

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Contributors TK contributed to the design and logistics of the protocol and wrote the manuscript. HI, as a corresponding author, TS, YS and MI proposed the concept and idea for Rescue study, drafted the protocol design of the study and proof-read the manuscript. TM contributed to the design and logistics of the protocol and proof-read the manuscript. GO contributed to the design and logistics of the protocol and proof-read the manuscript as a statistician. MI, KS, YI and RK contributed to design of the protocol and proof-read the manuscript. YK and MM contributed to the design and logistics of the protocol and proof-read the manuscript, and conducted the initiation of the study.

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Competing interests KS reports grants from reports research funding from Chugai.

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