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Clinical Trial Note

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A randomized controlled trial comparing primary tumour resection plus chemotherapy with chemotherapy alone in incurable stage IV colorectal cancer: JCOG1007 (iPACS study)

Konosuke Moritani[1], Yukihide Kanemitsu[1,*], Dai Shida[1], Kohei Shitara[2], Junki Mizusawa[3], Hiroshi Katayama[3], Tetsuya Hamaguchi[4], Yasuhiro Shimada[5], on behalf of the Colorectal Cancer Study Group (CCSG) of Japan Clinical Oncology Group (JCOG)

[1]Department of Colorectal Surgery, National Cancer Center Hospital, Tokyo, Japan, [2]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Tokyo, Japan, [3]JCOG Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan, [4]Department of Gastroenterology, Saitama Medical University International Medical Center, Saitama, Japan, and [5]Clinical Oncology Division, Kochi Health Sciences Center, Kochi, Japan

*For reprints and all correspondence: Yukihide Kanemitsu, Department of Colorectal Surgery, National Cancer Center Hospital, MD, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: ykanemit@ncc.go.jp

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Abstract

It is controversial whether chemotherapy with or without primary tumour resection is effective for the patients with incurable Stage IV colorectal cancer. A randomized controlled trial, initiated in Japan in 2012, is being conducted to evaluate the survival benefit and safety of primary tumour resection plus chemotherapy compared with chemotherapy alone in asymptomatic Stage IV colorectal cancer patients with unresectable metastatic disease. Patients are randomly assigned to either chemotherapy alone or primary tumour resection followed by chemotherapy. The primary endpoint is overall survival. Secondary endpoints are progression-free survival, incidence of adverse events, proportion of patients with R0 resection and proportion of palliative surgery for the chemotherapy-alone group. This trial was registered in June 2012 with the UMIN Clinical Trials Registry as UMIN000008147 [http://www.umin.ac.jp/ctr/index-j.htm]. In December 2017, the study protocol was amended for reducing sample size. A total of 280 patients will be enrolled over the course of 8.5 years.

Key words: colorectal cancer, randomized controlled trial, incurable, primary tumour resection, stage IV

Background and rationale

Colorectal cancer (CRC) is one of the major leading causes of death from cancer worldwide (1). With the introduction of new chemotherapeutic agents, survival of Stage IV CRC patients has improved substantially. However, at the time of diagnosis, the majority of patients with Stage IV disease have unresectable tumours and can only undergo palliative treatment. For patients with a symptomatic primary tumour (e.g. anaemia, obstruction and infection), surgical resection or a diverting stoma may be necessary. For patients with both unresectable metastatic disease and an asymptomatic primary tumour, the initial treatment strategy is controversial. Some have reported that the benefits of primary tumour resection on overall

Table 1. Randomized controlled trials (RCTs) for primary tumour resection (PTR) in incurable Stage IV colorectal cancer patients

Trial/name	Origin	Trial No.	Primary outcome	Semple size	Study start date	Est. study completion date	Status
SYNCHRONOUS[8]	Germany	ISRCTN30964555	OS, 3 yrs	800 → 392	Jan 11	Dec 19	*Ongoing/no longer recruiting
CAIRO4[9]	The Netherlands	NCT01606098	OS, 5 yrs	360	Jul 12	Aug 20	Recruiting
CCRe-IV[10]	Spain	NCT02015923	OS, 2 yrs	336	Dec 13	Nov 18	*Ongoing/no longer recruiting
CLIMAT[11]	France	NCT02363049	OS, 2 yrs	278	Jul 14	Jul 18	Recruiting
PTR Trial[12]	Korea	NCT01978249	OS, 2 yrs	480	Nov 13	Sep 16	**Early terminated
China multicenter[13]	China	NCT02149784	OS, 3 yrs	480	Sep 15	Jul 19	Recruiting
JCOG1007	Japan	UMIN000008147	0S, 3 yrs	770 → 280	Jun 12	Dec 20	Recruiting

*SYNCHRONOUS and CCRe-IV trails are ongoing and participants are receiving an intervention or being examined, but potential participants are not currently being recruited or enrolled.
**PTR trial was already early terminated because of the difficulties of participant enrolment.

survival are unclear and that morbidity and mortality related to tumour resection should be avoided because a delay in initiating chemotherapy can have a negative impact on survival (2,3). However, others have reported that the strategy for managing CRC patients with unresectable metastases is based on the beneficial effects of chemotherapy on both metastatic disease and the primary tumour in patients with good performance status (3, 4).

Conversely, many studies reported that resection of primary tumour is necessary in patients with unresectable distant metastases and an asymptomatic primary tumour (5, 6). Primary tumour resection could prevent intestinal complications, such as obstruction, bleeding, perforation or fistula (6). These complications are associated with poor oncologic outcomes as well as perioperative morbidity and mortality. Moreover, recent papers have reported significantly better overall survival for patients undergoing primary tumour resection than patients who do not have this treatment (5). Stillwell et al. reported that there is an improvement in the survival of patients managed with palliative resection of their primary tumour, with an estimated standardized median difference of 6.0 months by meta-analysis based on eight retrospective studies (HR = 0.55; 95% confidence interval (CI), 0.29–0.82; $P < 0.001$) (7).

However, previous studies support each opposing conclusion, and these studies are all retrospective. There is still considerable uncertainty if CRC patients who present with incurable disease and little or no symptoms should undergo resection of the primary tumour prior to systemic therapy. A randomiz'ed controlled trial is required for this reason. Thus, we have designed a clinical trial. At about the same time or later when we started this trial, there is much anticipation regarding the results of several ongoing randomized controlled trials, which are summarized in Table 1 (i.e. SYNCHRONOUS in Germany (8), CAIRO4 in the Netherlands (9), CCRe-IV in Spain (10), CLIMAT in France (11), PTR Trial in Korea (12), Multicenter trial in China (13)). Thus, elucidating clinical significance of primary tumour resection for this patient population is an important unmet need worldwide.

Our hypothesis for the trial is that primary tumour resection for incurable Stage IV CRC in asymptomatic patients might improve compliance with the protocol treatment, helping to prevent adverse events of chemotherapy and improve survival compared with chemotherapy alone. Compared with irinotecan regimen or combination regimen with cetuximab, the rationale for choosing mFOLFOX or CapeOX plus bevacizumab as the treatment arm for this trial is based on the results from previous studies that targeted incurable Stage IV patients (14). Oxaliplatin-based therapy is already a standard first-line treatment for metastatic unresectable CRC and is the most convenient of available regimens as it can be administered on an outpatient basis (15).

The study protocol was designed by the Colorectal Cancer Study Group of the Japan Clinical Oncology Group (JCOG) and was approved by the JCOG Protocol Review Committee in April 2012. This trial was registered in June 2012 with the UMIN Clinical Trials Registry as UMIN000008147 (http://www.umin.ac.jp/ctr/index-j.htm). Here we provide details on the amended protocol after monitoring in December 2017 (see "Protocol Amendment").

Protocol digest of JCOG1007

Purpose

The purpose of this trial was to confirm the superiority of primary tumour resection plus chemotherapy to chemotherapy alone in asymptomatic Stage IV CRC patients with synchronous incurable metastatic disease.

Study setting

This trial is a multi-institutional, randomized controlled phase III trial.

Endpoints

The primary endpoint is overall survival, defined as the time from randomization to death from any cause, and secondary endpoints are progression-free survival, incidence of adverse events, proportion of patients with R0 resection and proportion of patients with palliative surgery. Adverse events and postoperative complications were assessed in accordance with the Common Terminology Criteria for Adverse Events (version 4.0).

Eligibility criteria

CRC is classified according to the seventh edition of the Japanese Classification of Colon and Rectal Carcinoma (16) and the seventh edition of TNM classification (17). Prior to enrolment in this trial, patients must meet all of the following criteria:

(i) Pathologically proven adenocarcinoma or adenosquamous carcinoma.

(ii) Primary tumour located in the caecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectosigmoid colon or upper rectum.
(iii) Patients without obstruction due to a tumour must meet all of the following criteria:

A) **Oral intake ability**
B) **Ability to release gas**
C) No abdominal distension
D) No abnormal gas on X-ray
E) No prior evacuation treatment such as stent placement or stoma

(iv) No active bleeding and fistula or perforation.
(v) At least one unresectable factor below and no more than four factors on computed tomography (CT) or magnetic resonance imaging (MRI):

A) Unresectable hepatic metastasis
B) Unresectable pulmonary metastasis or malignant pleural effusion (including pneumoconiosis)
C) Distant lymph node metastasis (para-aortic, hepatic or mediastinal lymph node)
D) Peritoneal metastasis (not localized)

(vi) No sign of tumour invasion to other organs on abdominal CT.
(vii) No ascites in the pelvic cavity in preoperative examination.
(viii) No brain or bone metastasis.
(ix) Performance status (PS) 0 or 1 on Eastern Cooperative Oncology Group (ECOG) criteria.
(x) Aged 20–74 years.
(xi) No prior chemotherapy or radiotherapy.
(xii) Adequate organ function as evidenced by the following laboratory findings within 28 days prior to enrolment:

A) Neutrophil count $\geq$1500/mm^3
B) Platelet count $\geq$100 000/mm^3
C) Haemoglobin $\geq$9.0 g/dL (no transfusion within 4 weeks)
D) Aspartate aminotransferase $\leq$100 IU/l
E) Alanine aminotransferase $\leq$100 IU/l
F) Total bilirubin $\leq$2.0 mg/dl
G) Creatinine $\leq$1.5 mg/dl
H) PT-INR $\leq$ 1.5

(xiii) No symptoms of more than grade 2 for the following (CTCAE ver4.):

A) Diarrhoea
B) Peripheral sensory neuropathy

(xiii) Written informed consent.

Exclusion criteria

Prior to enrolment in this trial, patients must not meet any of the following criteria:

(i) Synchronous or metachronous (within 5 years) malignancies other than carcinoma *in situ* or mucosal carcinoma
(ii) Infectious disease requiring systemic therapy
(iii) Positive for hepatitis B (HB) surface antigen
(iv) Body temperature $\geq$ 38°C
(v) Pregnant, possibly pregnant or breastfeeding
(vi) Severe mental disorder
(vii) Currently treated with systemic steroids or immunosuppressive agents
(viii) Interstitial pneumonia, pulmonary fibrosis or severe emphysema
(ix) Uncontrolled diabetes mellitus or routine administration of insulin
(x) Uncontrolled hypertension, systolic blood pressure $>$ 150 mmHg or diastolic blood pressure $>$ 100 mmHg under medication
(xi) Heart dysfunction of class III or IV by New York Heart Association criteria or medication to prevent lethal ventricular arrhythmia
(xii) Abdominal fistula, perforation and abscess within the past 6 months
(xiii) Unstable angina, myocardial infarction, pulmonary infarction and deep venous thrombosis, cerebral haemorrhage, cerebral infarction, transient brain ischaemia or cerebrovascular disorder within the past 6 months
(xiv) Aortic aneurysm or dissection (thoracic, $\geq$6 cm, abdominal, $\geq$5 cm)
(xv) Congenital haemorrhagic diathesis or coagulopathy due to platelet or coagulation factor dysfunction (excluding coagulopathy due to preventive anticoagulation therapy)
(xvi) Haemoptysis within 28 days of registration

Randomization

Following confirmation of eligibility using the web-based system of the JCOG Data Center, patient is randomized to either chemotherapy alone or primary tumour resection followed by modified FOLFOX6 (mFOLFOX6) plus bevacizumab or CapeOX plus bevacizumab. The minimization method is used for the randomization of patients, thereby balancing the arms of the study according to institution, sex (male vs female), tumour location (colon and RS vs Ra) and performance status (0 vs 1).

Treatment methods

Chemotherapy-alone group. mFOLFOX or CapeOX regimen is selected individually before randomization with using the web-based system of the JCOG Data Center.

One course of mFOLFOX6 plus bevacizumab consists of an intravenous injection of bevacizumab 5 mg/kg over more than 10 minutes and oxaliplatin 85 mg/m^2 with leucovorin 200 mg/m^2 over 2 h followed by a fluorouracil 400 mg/m^2 bolus and 2400 mg/m^2 continuous infusion over 46 h repeated every 2 weeks. The course of CapeOX plus bevacizumab consists of an intravenous injection of bevacizumab 5 mg/kg over more than 10 minutes, oxaliplatin 130 mg/m^2 over 2 h and oral intake of capecitabine 1000 mg/m^2 twice a day for 14 days repeated every 3 weeks.

Primary tumour resection followed by chemotherapy group

After primary tumour resection, postoperative chemotherapy with mFOLFOX6 (or CapeOX) plus bevacizumab will be initiated between days 8 and 56 after surgery and repeated every 2 weeks (or 3 weeks), in the same manner as described for the chemotherapy-alone group (Fig. 1).

Follow-up

Patient is followed up every 8 weeks until disease progression or death. Follow-up evaluations include a clinical examination, blood

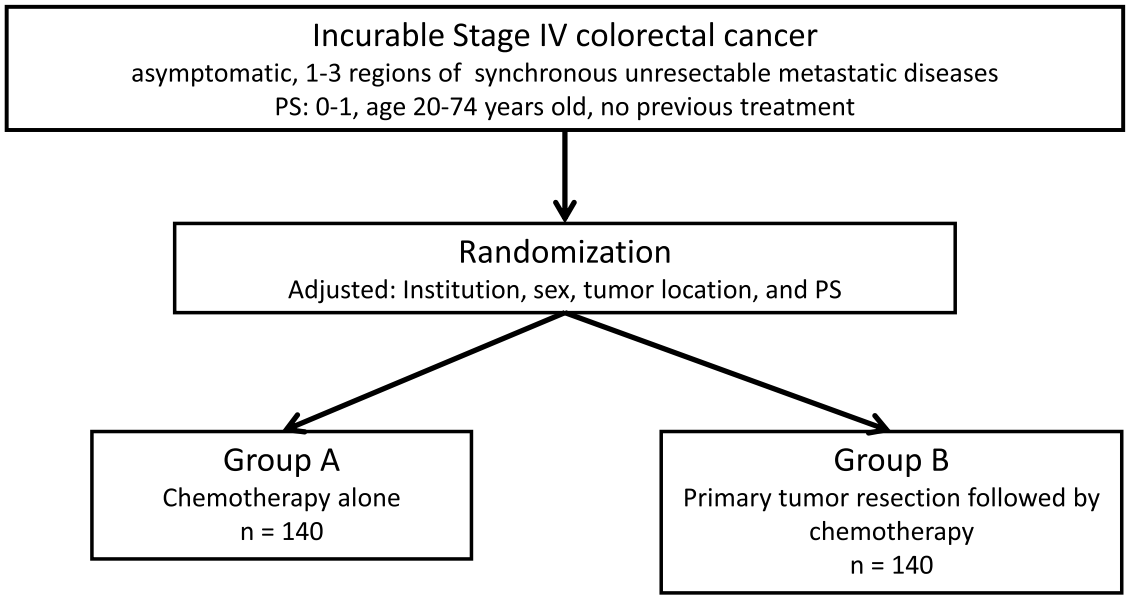

Figure 1 Flow diagram of the JCOG 1007 protocol.

cell count, serum chemical tests, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) as tumour marker tests and enhanced thoracic and abdominal/pelvic CT at 8-week intervals.

Study design and statistical methods (at the initiation of the study)

This trial is designed to confirm the superiority of primary tumour resection followed by chemotherapy to chemotherapy alone in terms of overall survival. At the initiation of the study, we hypothesized that the median survival time (MST) of the primary tumour resection and postoperative chemotherapy arm will be greater than that of the chemotherapy-alone arm of 20 months by 4 months (hazard ratio = 0.83). If the OS is significantly longer with primary tumour resection and postoperative chemotherapy compared with chemotherapy alone, primary tumour resection will be recommended as the standard treatment for incurable Stage IV colorectal cancer. According to the method of Schoenfeld and Richter (18), the required sample size will be 758 patients (379 patients per arm), with a one-sided alpha level of 5% and a power of 75% and with 647 events expected to occur during the 5 years of accrual and the 3 years of follow-up. Given that some patients will likely be lost to follow-up, the total target sample size is set at 770 patients.

However, as of October 2017, 5 years and 4 months after the beginning of enrolment, only 18.6% (143 of 770) patients had been enrolled, and at this pace, it would take more than 15 years to reach the enrolment goal. Therefore, we reviewed the study design, including the likelihood of study completion, and concluded that the following amendments could be made:

(1) Change the add-on effect of the test treatment on the standard treatment from 4 to 8 months based on two similar overseas studies, the CAIRO4 (Holland) (12) and the SYNCHRONOUS (Germany) study (11) and recommended add-on effect of the test treatment on the standard treatment standard difference (19, 20).
(2) Change the MST of the standard treatment group from 20 to 24 months because it became relevant that MST of the standard treatment was higher than expected.
(3) Change the power from 75 to 70% considering the feasibility.

The required sample size of 268 was calculated with hazard ratio of 0.75, which corresponded to MST of 24 months vs. 32 months, an accrual period of 7 years (1.5-year extension), a follow-up period of 3 years, α = 5% (one-sided) and a power of 70%. Although the required sample size is 268 patients (227 events) in total in both groups, the planned sample size is 280 considering a few lost follow-up patients.

Interim analysis and monitoring

We plan to conduct two interim analyses. The first interim analysis will be conducted after half of the planned number of patients has been enrolled. The second interim analysis will be conducted after the completion of patient accrual. The multiplicity will be adjusted using the Lan–DeMets method with the O'Brien- and Fleming-type alpha-spending function (21). The Data and Safety Monitoring Committee of the JCOG will independently review the interim analysis reports and determine if the trial should be terminated early. The JCOG Data Center and study coordinator will conduct central monitoring and 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 (not on a study-specific basis but for the study group).

Clinical trials registry

This trial was registered with the UMIN Clinical Trials Registry as UMIN000008147 (http://www.umin.ac.jp/ctr/index-j.htm).

Participating institutions (in order of geographical location from north to south Japan)

Sapporo-Kosei General Hospital, Iwate Medical University, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Tochigi

Cancer Center, Gunma Prefectural Cancer Center, National Defense Medical College, Saitama Medical University International Medical Center, Saitama Cancer Center, Jichi Medical University Saitama Medical Center, Saitama Medical Center, National Cancer Center Hospital East, Chiba Cancer Center, Juntendo University Urayasu Hospital, National Cancer Center Hospital, Kyorin University School of Medicine, Tokyo Medical University Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Keio University Hospital, Tokyo Medical and Dental University Hospital, Toho University School of Medicine Ohashi Hospital, Kitasato University East Hospital, Kanagawa Cancer Center, Yokohama Municipal Citizen's Hospital, Kitasato University Hospital, Showa University Northern Yokohama Hospital, Yokohama City University Medical Center, Saiseikai Yokohamashi Nanbu Hospital, Hiratsuka City Hospital, Niigata Cancer Center Hospital, Nagaoka Chuo General Hospital, Ishikawa Prefectural Central Hospital, Nagano Municipal Hospital, Gifu University School of Medicine, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Fujita Health University, Aichi Medical University Hospital, National Hospital Organization Kyoto Medical Center, Osaka University Faculty of Medicine, Osaka Red Cross Hospital, Osaka International Cancer Institute, Osaka National Hospital, Osaka General Medical Center, Osaka City General Hospital, Osaka Medical College, Sakai City Hospital, Minoo City Hospital, Suita Municipal Hospital, Kansai Rosai Hospital, Hyogo College of Medicine, Sano Hospital, Shimane University Faculty of Medicine, Okayama Saiseikai General Hospital, Hiroshima City Hospital, Hiroshima Prefectural Hospital, Fukuyama City Hospital, Hiroshima City Asa Hospital, National Hospital Organization Shikoku Cancer Center, Kochi Health Science Center, Kurume University School of Medicine, Kumamoto University School of Medicine and Oita University Hospital. Approval by the institutional review board of each institution was obtained prior to patient accrual.

Conflict of interest statement

K.M. has no conflict of interest. Y.K. has no conflict of interest. D.S. has no conflict of interest. K.S. reports personal fees from Yakult and research funding from Chugai. M.J. has no conflict of interest. K.H. has no conflict of interest. T.H. reports personal fees from Yakult and Chugai. Y.S. reports personal fees from Yakult and Chugai.

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