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A Randomized Controlled Trial of the Conventional Technique Versus the No-touch Isolation Technique for Primary Tumor Resection in Patients with Colorectal Cancer: Japan Clinical Oncology Group Study JCOG1006

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A randomized controlled trial is currently being conducted in Japan to demonstrate the superiority of the no-touch isolation technique over the conventional technique for patients with potentially curative colon and rectosigmoid cancer. The conventional technique procedure gives first priority to mobilization of the tumor-bearing segment of the colon, which is followed by central vascular ligation and ligation of other vasculature. Conversely, the no-touch isolation technique gives first priority to central vascular ligation, which is followed by mobilization of the tumor-bearing segment of the colon. A total of 850 patients will be enrolled in this trial. The primary endpoint is disease-free survival. Secondary endpoints are overall survival, relapse-free survival, liver metastasis-free survival, mode of recurrence, surgical morbidity, adverse events due to postoperative chemotherapy, serious adverse events and short-term clinical outcomes.

Key words: colorectal cancer – randomized controlled trial – conventional technique – no-touch isolation technique

BACKGROUD AND RATIONALE

Colorectal cancer is one of the main causes of cancer deaths in Japan and the West, and the incidence of colorectal cancer has been increasing in Japan (1). Patients with colorectal cancer have good prognosis after curative resection. Total mesorectal excision (2–5) and complete mesocolic excision (CME) (6) for rectal and colon cancers, respectively, reduce recurrence after curative resection. Further, Japanese D3 dissection is confirmed to be a similar surgical procedure to CME (7). Although these are valuable treatment options, an improved surgical technique to further reduce the incidence of recurrence would be beneficial. The no-touch isolation technique (NTIT) was first proposed in the 1950s (8). The NTIT gives first priority to central vascular ligation, which is followed by mobilization of the tumor-bearing segment of the colon. This technique aims to reduce cancer cells flowing from the primary tumor site to liver and other organs by ligating blood vessels first. A retrospective study showed improvement in prognosis with this technique (9), but a randomized controlled trial (RCT) failed to prove its efficacy with statistical significance (10). Therefore, the NTIT is not regarded as a standard technique in the current guidelines.

However, upon review of the RCT details, we concluded that the RCT could not show the superiority of NTIT because of insufficient sample size and many patients being lost to follow-up (10). Therefore, we initiated a large-scale RCT to confirm the utility of the NTIT in patients with colorectal cancer.

STUDY PROTOCOL

Purpose

The aim of this trial was to demonstrate the superiority of the NTIT over the conventional technique in disease-free survival of patients with potentially curative, advanced colon and rectosigmoid cancers.

Study Setting

This trial is a multi-institutional, prospective, open-label, randomized phase III trial.

Resources

This trial is supported by the National Cancer Research and Development Fund (23-A-16, 23-A-19).

Endpoints

The primary endpoint of this trial is disease-free survival. Disease-free survival is defined as the time from randomization to the first evidence of relapse, second primary cancer or death from any cause. Secondary endpoints are overall survival, relapse-free survival (with relapse and death as events), liver metastasis-free survival (with liver metastasis and death as events), mode of recurrence, surgical morbidity, adverse events due to postoperative chemotherapy, serious adverse events (Grade 4 non-hematological toxicity, early death within 30 days after protocol treatment or treatment-related death) and short-term clinical outcomes (time to first flatus after surgery, the proportion of analgesic use, the highest body temperature in the first 3 days following surgery and the highest body temperature during hospitalization).

Eligibility Criteria

Inclusion Criteria

Prior to enrollment in this trial, patients must fulfill all of the following criteria:

(i) Pathologically proven adenocarcinoma (including mucinous and signet-ring cell) or adenosquamous carcinoma on endoscopic biopsy;
(ii) Tumor localization at the cecum (C), ascending colon (A), transverse colon (T), descending colon (D), sigmoid colon (S) or rectosigmoid (RS) on preoperative endoscopy and radiographic imaging [barium enema or computed tomography (CT)] without location of the lower border of the tumor at the rectum;
(iii) Tumor depth of either SS, SE, SI, A or AI; nodal metastasis of either N0, N1 or N2; and neither H0, P0 nor M0 on preoperative radiographic imaging;
(iv) No multiple colorectal cancers;
(v) Age range of 20–80 years;
(vi) Eastern Cooperative Oncology Group performance status, 0 or 1;
(vii) No prior chemotherapy or radiotherapy for any malignancies;
(viii) Sufficient organ function;
(ix) Body mass index, <30;
(x) No history of intestinal resection, serious obstruction or perforation;
(xi) No history of familial adenomatous polyposis, ulcerative colitis or Crohn's disease;
(xii) Written informed consent.

Exclusion Criteria

Prior to this trial, patients must not fulfill any of the following criteria:

(i) Synchronous or metachronous (within 5 years) double cancers;
(ii) Infectious disease requiring treatment;
(iii) Body temperature of 38°C or higher;
(iv) Pregnant or breast feeding women;
(v) History of psychiatric disease;
(vi) Use of systemic and continuous steroids;
(vii) History of myocardial infarction or unstable angina pectoris within 6 months;
(viii) Severe pulmonary emphysema or pulmonary fibrosis.

Randomization

Following confirmation of the eligibility of patients via internet, telephone or fax to the JCOG Data Center, patients are randomized to either the conventional technique arm or the NTIT arm of the study. The minimization method is used for the randomization of patients, thereby balancing the arms of the study according to the location of the colon cancer (C, A, T/D, S, RS), sex and institution.

Treatment Methods

Colorectal carcinoma in both arms is classified according to the seventh edition of the Japanese Classification of Colorectal Carcinoma (11), and Japanese D3 dissection, including central vascular ligation, intestinal transection and lymph node dissection, is performed. The extent of resection of the intestine and the position of the central vascular ligation for dissection of the lymph nodes do not differ between arms. Anastomosis for intestinal reconstruction is not specified.

In the conventional technique arm, the first step of the operation comprises the mobilization of the tumor-bearing

segment. This is performed before any vessels are ligated. In the NTIT arm, the first step of the operation comprises central vascular ligation. Subsequently, marginal vessel ligation, intestinal transection and mobilization of the tumor-bearing segment are performed.

When patients are diagnosed with pathological Stage III disease after curative resection, postoperative adjuvant chemotherapy with capecitabine is administered for 6 months.

Follow-up Analyses

Patients will be followed-up every 3 months until the third year, and subsequently, every 6 months until the sixth year. Follow-up analyses include clinical examination, tumor marker-level determination [carcinoembryonic antigen (CEA) and cancer antigen (CA) 19-9] and thoracic/abdominal/pelvic computed tomography.

Study Design and Statistical Methods

This trial is designed to confirm the superiority of the NTIT over the conventional technique in terms of disease-free survival. We hypothesize that the 3-year disease-free survival of the NTIT arm will be greater than that of the conventional technique arm (75%) by 6%. If a statistically significant improvement in disease-free survival is demonstrated, the NTIT will be the new standard technique. According to the method of Schoenfeld and Richter (12), the sample size in this trial will be 840 patients (420 patients per arm), with a one-sided alpha level of 5% and power of 80%, and 259 events are expected to occur within 3 years of accrual and 3 years of follow-up. Considering some patients will be lost to follow-up, the total target sample size is set at 850 patients.

Interim Analysis and Monitoring

We plan to conduct two interim analyses, taking multiplicity into account, using the Lan-DeMets method with the O'Brien and Fleming-type alpha spending function. The Data and Safety Monitoring Committee of the JCOG will independently review the interim analysis reports and terminate the trial prematurely if necessary.

In-house monitoring will be performed every 6 months by the JCOG Data Center to evaluate and improve the progress and quality of the study.

UMIN Clinical Trials Registry

This trial was registered at the UMIN Clinical Trials Registry (www.umin.ac.jp/ctr/) as UMIN000004957.

PARTICIPATING INSTITUTIONS (LISTED FROM NORTH TO SOUTH)

Sapporo-Kosei General Hospital, Iwate Medical University Hospital, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Tochigi Cancer Center, Gunma Prefectural Cancer Center, National Defense Medical College Hospital, Saitama Cancer Center, Saitama Medical University International Medical Center, National Cancer Center Hospital East, Chiba Cancer Center, National Cancer Center Hospital, Kyorin University Hospital, Tokyo Medical University Hospital, Toho University Ohashi Medical Center, Kanagawa Cancer Center, Yokohama City University Medical Center, Saiseikai Yokohamashi Nanbu Hospital, Niigata Cancer Center Hospital, Nagaoka Chuo General Hospital, Ishikawa Prefectural Central Hospital, Nagano Municipal Hospital, Gifu University Hospital, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka National Hospital, Osaka General Medical Center, Sakai City Hospital, Minoh City Hospital, Suita Municipal Hospital, Kansai Rosai Hospital, Osaka General Medical Center, Hyogo College of Medicine Hospital, Sano Hospital, Okayama Saiseikai General Hospital, Hiroshima Prefectural Hospital, Shikoku Cancer Center, Kochi Health Sciences Center, Kurume University Hospital, Kumamoto University Hospital and Oita University Hospital.

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Conflict of interest statement

None declared.

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