12. Confirmation of recurrence and Endpoint definition

12.1. Definition of relapse and the date of relapse

Define either of the following situations as relapse.

1) When any modality of image (chest X-ray, ultrasonography, computed tomography, magnetic resonance imaging) reveal relapse, the date of examination is regarded as event date. If more than 2 modalities reveal relapse, the oldest date of examination is regarded as event date.
2) When we judge relapse clinically without confirmation of image, the date of judgment is regarded as event date. The objective findings indicating relapse should be recorded on medical record and case report form (CRF).
3) When relapse is not confirmed by image or clinical judgment but confirmed by cytology or biopsy, the oldest date of examination is regarded as event date.

12.2. Definition of local relapse and the date of local relapse

We diagnose as local relapse if the criteria of relapse described in "12.1." is fulfilled and either of following situations are fulfilled.

1) When the pelvic CT reveals that a new leasion locate in the pelvic space (including pelvic bone), we diagnose the lesion as local relapse. If a new lesion locates in small intestine or cecum, we do not diagnose the lesion as local relapse.
2) When a tumor is palpable by digital examination, we diagnose it as local relapse.

When a relapse is found in distant area but local relapse is not found, the date of the other relapse is not censored and we keep on follow-up. When direct invasion from distant area to local area is observed, the date of diagnosis for direct invasion is regarded as event date of local relapse.

12.3. Definition of analyzed patients

12.3.1. All registered patients

Populations excluding double registration and false registration from patients registered according to 6. 1 'Registration procedure' are defined as "all registered patients".

12.3.2. All eligible patients

Populations excluding "ineligible patients" determined by the Study Group from all registered patients are defined as "all eligible patients". The "ineligible patients" judged only by institutional physicians are not regarded as ineligible formally. Approval by the Group Chair is necessary for the final decision of the "ineligible patients"; however, for interim analysis, regular interim monitoring, or analysis for a presentation at a meeting of the society before the final analysis report is fixed, the JCOG data center and the study coordinator can determine tentative "Ineligible patients".

12.3.3. All postoperative chemotherapy treated patients

Populations who received any part of postoperative chemotherapy among all registered patients are defined as all postoperative chemotherapy treated patients.

12.4. Endpoint definition

12.4.1. Relapse-free survival (RFS)

Relapse-free survival is counted from the date of registration to the date of earliest one among the following events.

Event	Event date
1. Death from any cause	Date of death
2. Relapse (including local relapse)	Date of diagnosis as relapse

- When any of the events above is not observed, RFS is censored at the latest visit to hospital.
- When the pathological result reveal surgical margin is positive, protocol treatment is terminated on the first operation date which is regarded as event date.
- When multiple colon cancer located in the proximal side from primary tumor is found by colonoscope after surgery,
  - ✓ If patients undergo surgery, protocol treatment is terminated on the second operation date which is regarded as event date.
  - ✓ If patients are treated by endoscopic resection and considered as curative resection, they are still regarded as progression-free (neither PFS event nor censored).
- When protocol treatment is terminated because of toxicity and patient refusal, they are still regarded as progression-free (neither PFS event nor censored).

12.4.2. Local relapse-free survival

Local relapse-free survival is counted from the date of registration to the date of earliest one among the following events. Relapse except local relapse is not regarded as event and is not censored.

Event	Event date
1. Death from any cause	Date of death
2. Local relapse.	Date of diagnosis as local relapse

- When any of the events above is not observed, RFS is censored at the latest visit to hospital.
- When the pathological result reveal surgical margin is positive, protocol treatment is terminated on the first operation date which is regarded as event date.
- When protocol treatment is terminated because of toxicity and patient refusal, they are still regarded as progression-free (neither PFS event nor censored).

12.4.3. Overall survival

Overall survival is measured from the date of registration (randomization) to the date of death from any cause.
Surviving patients and patients lost to follow-up are censored at the latest contact date.

Event	Event date
1. Death from any cause	Date of death

12.4.4. Proportion of adverse events

Proportion of intraoperative and postoperative morbidity

Among all registered patients, frequencies of the worst grade of the following adverse events are calculated in both arms as intraoperative and postoperative morbidity according to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0 and JCOG surgical morbidity criteria.

1) Intraoperative morbidity (From start to finish of an operation)
   - Bleeding: associated with surgery (more than 500 cc bleeding is defined as grade 1 or higher)
   - Cardiovascular: Thrombosis / Embolism
   - Renal / Genitourinary: Surgical injury of bladder / ureter
   - Other fatal morbidity

2) Postoperative morbidity (From finish of an operation to discharge)
   - Constitutional symptoms: Fever
   - Anastomotic leak, Pelvic abscess
   - Skin: Wound complication-infectious
   - Bleeding: Melena / Gastrointestinal hemorrhage

- Cardiovascular: Thrombosis / Embolism
- Gastrointestinal: rectal / anal fistula, intestinal fistula
- Gastrointestinal obstruction
- Renal / Genitourinary: urinary frequency / urgency, urinary retention, ureteral obstruction
- Infection: infection without neutropenia

3) Postoperative late morbidity (From discharge to 5 years after surgery)
   - Gastrointestinal: Constipation, Diarrhea
   - Lymphatics: Lymphatics
   - Renal / Genitourinary: urinary frequency / urgency, urinary retention, ureteral obstruction
   - Sexual / Reproductive function: Erectile impotence, Libido
   - Gastrointestinal obstruction

Proportion of adverse event of postoperative chemotherapy
Among all patients treated by postoperative chemotherapy, frequencies of the worst grade of the following adverse events are summarized based on NCI-CTC version 2.0. Each of the adverse events is reported from the first date of chemotherapy to 4 weeks after the last administration of chemotherapy.

- Blood / Bone marrow: Hemoglobin, Leukocytes, Neutrophils, Platelets
- Constitutional symptoms: Fever
- Dermatology / Skin: Hand-foot skin reaction, Pigmentation changes
- Gastrointestinal: Anorexia, Diarrhea, Nausea, Sense of smell, Stomatitis / pharyngitis, Taste disturbance, Vomiting
- Hepatic: Bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT)
- Infection / Febrile neutropenia: Febrile neutropenia, Infection with grade 3 or 4 neutropenia, Infection without neutropenia
- Metabolic / Laboratory: Hypernatremia, Hyponatremia, Hyperkalemia, Hypokalemia
- Neurology: Neuropathy-motor
- Renal / Genitourinary: Creatinine

12.4.5. Proportion of serious adverse event
Determined as the proportion of serious adverse events which fulfill any of the following events among all registered patients.
1) Any death during protocol treatment or within 30 days after surgery or the last date of chemotherapy
2) Death after 31 days from surgery or the last date of chemotherapy with attribution of possible, probable, definite
3) Grade 4 non-hematological toxicity

12.4.6. Operation time
Time from start to finish of an operation in all registered patients.

12.4.7. Blood loss (ml)
Total amount of blood loss during the operation in all registered patients.

12.4.8. Proportion of (incidence of) urinary dysfunction
Determined as the proportion of patients whose residual urine is 50ml or more among all eligible patients. The measurement method of residual urine is indicated in "9.2.6. Evaluation after surgery; method of residual urine measurement "
If patients can not measure residual urine at least 3 times, basically we include them in the numerator of urinary dysfunction. However, if patients measured residual urine less than

three, residual urine is 50ml or less in every measurement, and physician assesses them having normal urinary function, we do not include them in the numerator of urinary dysfunction.

12.4.9. Proportion of (incidence of)sexual dysfunction

Determined as the proportion of patients whose score is 21 or less one year after surgery among eligible male patients whose score of baseline International Index of Erectile Function 5 (IIEF5) is 22 or more. If sexual function is not evaluated because of their death or other reasons, we include them in the numerator of sexual dysfunction.

13. Statistical Consideration

13.1. Primary analysis and decision criteria

Primary endpoint is relapse-free survival (RFS). Secondary endpoints are overall survival (OS), local relapse-free survival, incidence of adverse events, incidence of serious adverse events, and incidence of sexual and urinary dysfunction.

The objective of primary analysis is to determine whether the test regimen (Mesorectal excision without lateral lymph node dissection, Arm B) is non-inferior to the standard regimen (Mesorectal excision with lateral lymph node dissection, Arm A) in the primary endpoint, relapse-free survival.

If Arm B is non-inferior to Arm A with a statistical significance in the primary endpoint, and superior in other endpoints, we conclude Arm B is better treatment.

If non-inferiority of Arm B to Arm A in the primary endpoint is not shown, or not superior in other endpoints, we conclude Arm A is still better treatment.

Other endpoints were incidence of adverse events, incidence of serious adverse events, incidence of sexual and urinary dysfunction, operation time, and blood loss.

Cox's proportional hazard model including treatment and adjustment factors which are used in randomization other than institution is performed in primary analysis for the eligible population which is determined with group review. Hazard ratio (HR) of Arm B to Arm A and confidence interval are used for the primary analysis. Wald-type confidence interval is used. Non-inferiority margin is set to 1.34, which is HR of Arm B to Arm A. As a sensitivity analysis, analyses with the all randomized population are also conducted.

Since this study is non-inferiority trial, one-sided test is used for the primary analysis. Study-wise type I error was set to a one-sided 5%. RFS curves, median relapse-survival time, and relapse-survival proportions for each year are estimated by the Kaplan-Meier method, and 95% confidence intervals are calculated using Greenwood's formula. Hazard ratios of the treatment effect and its 95% CI are estimated through the Cox's proportional hazard model. If necessary, background factors that are imbalance between arms can be considered as explanatory variables in the Cox regression analyses.

13.2. Planned sample size, accrual period, follow-up period

Based on "2.7. Clinical hypothesis and rationale for sample size determination", the estimated relapse-free survival of Arm A and Arm B from the previous studies are showed as a table below.

According to an expectation of patient accrual of Colorectal Cancer Surgical Group (CCSG) described in "2.4.2 Expectation of patient accrual", the sample size is calculated with a 5 year accrual period and a minimum follow-up of 5 years.

Under the assumption that incidence of adverse events, incidence of serious adverse events, incidence of sexual and urinary dysfunction, operation time, and blood loss of Arm B are less than Arm A, Arm B should not be inferior 8% or more to Arm A in terms of a %5-year relapse-free survival to be a new standard regimen .

Required sample size in each arm (one-sided alpha = 5%) to confirm whether the test arm regimen (Mesorectal excision without lateral lymph node dissection, Arm B) is non-inferior to the standard arm regimen is given as follow.

If %5-year relapse-free survival in Arm A are 65%, 70%, and 75%, an 8% decrease in the %5-year relapse-free survival for each corresponds to HRs, 1.31, 1.34, 1.39, respectively.

Because we consider HR 1.39 is too larg for a non-inferiority margin, we set 1.34 as a non-inferiority margin. Required sample size, as following table, were calculated for cases that %5-year relapse-free survivals in Arm A are 65%, 70%, and 75% and non-inferiority margin is 1.34.

Shaded cells of the table show scenarios which requires less than 300 patients in each arm.. If efficacy of arms is equal, statistical power more than 75% can be attained for a case that %5-year relapse-free survival in Arm A is 65%. In the same way, statistical power more than 70% can be attained for the case that %5-year relapse-free survival in Arm A is 70%.

Thus, planned total sample size is set at 600 patients in consideration of group's recruitment ability of patients.

If %5-year relapse-free survival in Arm A, however,, is more than 70%, statistical power may be insufficient with 300 patients each arm.

So, we are going to consider whether to increase sample size when %5-year relapse-free survival in all randomized patients is more than 70% at the timing of semiannual monitoring or interim analysis.

[Revised v1.6]
A first semester semiannual monitoring report in 2008 revealed that %5-year relapse-free survival in all randomized patients was 75%. This proportion was better than what we had assumed.
This study is intended to attain statistical power at least 70%, and if possible, more than 75%. However, statistical power may be fall below 70% with predetermined 600 patients.
Therefore, sample size and accrual period were re-evaluated and protocol was revised to v1.6 to keep sufficient statistical power.
If %5-year relapse-free survival of two arms are equal, with %5-year relapse-free survival of Arm A of 75% and accrual period is 6 years, 688 patients are required to keep statistical power of 75%. It is, however, difficult to complete accrual of 688 patients within 6 years considering an on-going accrual speed.
So we revised the accrual period as 7 years. Required sample size were re-calculated for scinarios that %5-year relapse-free survival in Arm A are 65%, 70%, and 75% and non-inferiority margin 1.34. The results are as follows.
Shaded cells of the table (less than 350 patients in each arm) revealed that we can expect statistical power of at least 75% if , if %5-year relapse-free survival of both arms are 75%.
Therefore, planned sample size was revised to 700 patients in the protocol v1.6.

13.3. Interim analysis and early termination of the trial

13.3.1. Objective and timing of the interim analysis

During the study period, planned interim analyses are performed twice to determine whether the primary objective of the trial is confirmed. The first interim analysis is conducted during accrual period to evaluate whether continuing accrual is adequate. The second interim analysis is conducted to decide whether the preplanned follow-up is necessary in terms of efficacy when all of the patients are registered. At each interim analysis, if it is evident that the trial's primary objective has been attaubed, the study will be closed and we will make a presentation and publish the results immediately.

The first interim analysis is conducted when a half of planned sample size has registered. The cutoff date for the analysis is determined by considering the timing of the first semiannual monitoring after the half of planned sample size has registered. The second interim analysis is conducted after the patient registration is finished and all of the protocol treatments are finished for the registered patients. The cut-off date for the analysis is determined by considering the timing of the semiannual monitoring by the JCOG data center and the study coordinator. During the interim analysis, patient accrual is continued.

13.3.2. Interim analysis methods

The endpoint of interim analysis and final analysis are relapse-free survival. To keep the study-wise significance level at a one-sided 5% and to adjust for multiplicity, the alpha spending function of Lan & DeMets is used. O' Brien & Fleming type boundary is used as alpha-spending function.

If Arm B is non-inferior to Arm A with a statistical significance in terms of the relapse-free survival, we subsequently conduct an analysis to determine whether Arm B is superiority to Arm A. Multiplicity adjustment for this comparison is not required. Because a statistical multiplicity problem does not occur to confirm superiority subsequently after non-inferiority had been confirmed for the relapse-free survival.

Interim analyses are performed in JCOG Data Center. If necessary, the group statistician for the CCSG in the data center prepares the Statistical Analysis Plan (SAP) before conducting the interim analysis.

In consequence of interim analysis, this study terminate if,

If Arm B is non-inferior to Arm A with a statistical significance, and is superior to Arm A

with a statistical significance in the relapse-free survival.
If a point estimate of hazard ratio of Arm B to Arm A, exceeds the non-inferiority margin (HR > 1.34).

In consequence of interim analysis, if Arm B is non-inferior to Arm A with a statistical significance, but is not superior to Arm A with a statistical significance in the relapse-free survival, this study will not terminate even though Arm B is superior to Arm A with a statistical significance in the secondary endpoints.
As described in "13.2 Planned sample size, accrual period, follow-up period", if %5-year relapse-free survival of Arm A is higher than 70%, planned sample size is not sufficient. So in such cases, sample size re-evaluation will be carried out based on data at that time under a blinded manner, i.e. without between arms comparison data.

13.3.3. Reporting and review of the interim analysis results

The results of interim analysis are reported exclusively to the Data and Safety Monitoring Committee (DSMC), who review the results and make a recommendation for the study coordinator as to whether the study should be continued or not. The members of the JCOG CCSG who are members of the JCOG DSMC will not join in the DSMC review of this study. The results of the interim analysis are provided only to the members of the DSMC, unless the committee makes an exceptional decision that it is necessary to inform to the investigators.

With the interim analysis report review, if the DSMC recommends stopping or amending the protocol, partially or totally, the principal investigator decides whether to accept the recommendation.

To stop or change a part of the trial, the principal investigator submits a study closure form or a protocol amendment form to the DSMC. With approval by the DSMC, the principal investigator can stop the trial or amend a part of the trial.

The principal investigator is allowed to file an objection against the recommendation by the DSMC. When the principal investigator and DSMC cannot agree, the JCOG chair makes the final decision.

13.4. Analysis for the secondary endpoints

13.4.1. Analysis for the secondary endpoints for safety

The secondary endpoints for safety are incidence of adverse events, incidence of serious adverse events, incidence of sexual dysfunction and urinary dysfunction, operation time, and blood loss. These endpoints except for incidence of sexual dysfunction and urinary dysfunction are evaluated and reported at every semiannual monitoring (see also Section 15.1). The incidence of sexual dysfunction and urinary dysfunction are analyzed at the interim analysis and final analysis. We expect that incidence of adverse events, incidence of serious adverse events, incidence of sexual dysfunction and urinary dysfunction, operation time, and blood loss of Arm B are lower than those of Arm A.

13.4.2. Analysis for the secondary endpoints for effectiveness

The secondary endpoints for efficacy are overall survival (OS) and local relapse-free survival, and analyses of these endpoints with between arms comparisons are conducted only at the interim analysis and final analysis. Multiplicity adjustments for the secondary endpoints will not be made. We expect that Arm B is non-inferior to Arm A in overall survival, and local relapse-free survival. As a sensitivity analyses, in addition to the primary analysis for the entire eligible population determined by the review by the group, comparison with all randomized patients are also carried out.

The local RFS curves, median local relapse-survival time, local relapse-survival proportions for each year, OS curves, median overall survival time, and overall survival proportions for each year are estimated with the Kaplan-Meier method, and 95% confidence intervals are calculated using Greenwood's formula. Cox's proportional hazard model including treatment, adjustment factors which are used in randomization, except for institution, is performed. Hazard ratio (HR) of Arm B to Arm A and confidence interval are used. If necessary, not only

adjustment factors in randomization but also background factors that are unbalanced between arms can be considered as explanatory variables in the Cox regression. Wald-type confidence interval is used. Non-inferiority margin 1.34, which is HR of Arm B to Arm A used for the primary endpoint, is used as reference to evaluate the non-inferiority of Arm B to Arm A in terms of locar RFS and OS.

13.5. Final analysis

At the end of the follow-up period, all endpoints are analyzed after the data fixation of final monitoring. Except for the interim analyses and the final analysis, analyses with between-arms comparisons for the primary and secondary endpoints for efficacy are not performed unless approved by the DSMC.

The final analysis report is prepared by the JCOG Data Center and submitted to the study coordinator, the principal investigator, CCSG chair, the principal investigator of the related research by Grants-in-Aid for Cancer Research, the Clinical Trial Review Committee and the JCOG chair.

The principal investigator and study coordinator will summarize the study result in the final analysis report and produce a Clinical Summary Report that includes conclusions, points to consider, explanations, a discussion and future directions with respect to the clinical aspects. With the approval of the JCOG-LSG chair, the report will be submitted to the JCOG Clinical Trial Review Committee, the JCOG data center and the JCOG Chair.

14. Ethical considerations

15. Monitoring

16. Special instructions

17. Organization

17.1. JCOG (Japan Clinical Oncology Group)

JCOG is a multicenter cancer cooperative group based on 6 major research grants (listed below) by Grants-in-Aid for Cancer Research from the Ministry of Labour and Welfare. This study is mainly based on 20S-3, and is conducted using the resouces in JCOG in compliance with JCOG rules established by JCOG Executive Committee.

20S-1 'Multi-institutional co-operative studies to establish the standard therapy for chemo-sensitive malignant tumors': Principal Investigator - Tomimitsu Hotta (National Hospital Organization Nagoya Medical Center)

20S-2 'Multi-institutional co-operative studies to establish the standard therapy for pulmonary malignant tumors': Principal Investigator – Nagahiro Saijo (National Cancer Center Hospital East)

20S-3 'Multi-institutional cinical study for establishing standard treatment in Gastrointestinal malignant tumors ': Principal Investigator – Yasuhiro Shimada (National Cancer Center Hospital)

20S-4 'Multi-institutional cinical study for establishing standard treatment in rare malignant tumors ': Principal Investigator – Soichiro Shibui (National Cancer Center Hospital)

20S-5 'Multi-institutional cinical study for establishing standard radiotherapy ': Principal Investigator – Masahiro Hiraoka (Kyoto University Hospital)

20S-6 'Study for Establishment of Multi-institutional Cooperative Research Mechanism': Principal Investigator – Haruhiko Fukuda (National Cancer Center)

The other research grants

Health Science Research Grants for Medical Frontier Strategy Research, Health and Labour Science Research Grants for Clinical Research for Evidenced Based Medicine and Health and Labour Science Research Grant for Clinical Cancer Research from the Ministry of Health, Labour and Welfare, Japan

JCOG Chari:

Nagahiro Saijo- National Cancer Center Hospital East

17.2. Study group

Colorectal Cancer Study Group (CCSG)
Group Chair: Yoshihiro Moriya (National Cancer Center)

17.3. Study chair

Shin Fujita (National Cancer Center)

17.4 Study coordinator

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17.5. Participating institutions

17.6. JCOG Clinical Trial Review Committee and Data and Safety Monitoring Committee

JCOG Clinical Trial Review Committee (current Protocol Review Committee)
This study protocol was reviewed and approved by this committee in advance to the review by the IRB in each particiapating institution.

JCOG Data and Safety Monotoring Committee (DSMC)
DSMC monitors the study after activation

17.7. Data Center

JCOG Data Center

(Clinical Information Section, Cancer Information and Epidemiology Division, Center for Cancer Prevention and Screening, National Cancer Center, and Tsukiji Branch of Clinical Research Data Center of the Society of Japanese Pharmacopoeia)

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Web : http://www.jcog.jp/
Director: Haruhiko Fukuda
Statistician: Naoki Ishizuka
Data manager: Harumi Kaba, Ayaka Nakano

18. Publication policy

Study Chair or the other members of CCSG make the publication in an appropriate scientific meeting and a journal in English. The name of the participating institutions and the site investigators are included in the publication.

19. References