Neoadjuvant Chemotherapy with CAPOX versus Chemoradiation for Locally Advanced Rectal Cancer with Uninvolved Mesorectal Fascia (CONVERT) : Initial Results of A Phase III Trial

**CLINICAL STUDY PROTOCOL**

This study is ongoing but not recruiting participants.

Study Start Date: August 2014

Primary Completion Date: May 2021

Estimated Study Completion Date: June 2024

|  |  |
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1. **Background and rationale**
   1. Background

Colorectal cancer (CRC) is one of the most common malignant tumors worldwide. According to the World Health Organization, CRC ranks third in male tumor incidence and ranks second in female tumor incidence. In 2008, there were approximately 1,200,000 newly diagnosed cases worldwide and 608,700 deaths from the disease. In recent years, with the changes in eating habits and dietary structure, and the aging of the population, the incidence and mortality of colorectal cancer in China have been increasing. In general, the incidence of colon cancer and rectal cancer is similar, while in some areas the proportion of rectal cancer is slightly higher than 50%.

The prognosis of rectal cancer is worse than that of colon cancer, and one of the important reasons is the high incidence of local recurrence after surgery, especially in locally advanced rectal cancer. Previously, the local recurrence rate of conventional surgery alone was reported to be 24-30%, and the 5-year survival rate to be 43-50%. In order to improve local control, Bill Heald proposed total mesorectal excision (TME) in 1982, which was believed to be effective in reducing local recurrence. Subsequently, many scholars confirmed that the local control rate of rectal cancer after TME was significantly lower compared with that of conventional surgery, ranging from 4-8%. Meanwhile, the perioperative radiotherapy has been shown to have better local control and tolerance than postoperative radiotherapy. Therefore, the National Comprehensive Cancer Network (NCCN) guidelines recommend "preoperative concurrent radiotherapy + TME" as the standard of care for locally advanced rectal cancer (clinical stages II and III), and recommend a 6-month perioperative treatment. Since then, preoperative radiotherapy concurrently with 5-fluorouracil±LV/capecitabine have been widely used in the treatment of locally advanced rectal cancer.

* 1. Rationale

Although preoperative radiotherapy combined with 5-fluorouracil/capecitabine is the standard of care for locally advanced rectal cancer, preoperative radiotherapy also has several unresolved drawbacks.

First, preoperative radiotherapy for rectal cancer does not improve patients’ long-term survival. As TME effectively reduces the local recurrence rate of resectable rectal cancer, the influence of distant metastasis on survival becomes more prominent. There may be micrometastasis at the time of diagnosis and obviously cannot be eliminated by TME or local radiotherapy. To date, no phase III clinical trials demonstrate survival benefit of preoperative radiotherapy. Therefore, many studies have attempted to combine preoperative radiotherapy with more intense concurrent chemotherapy and targeted agents, as well as induction chemotherapy before preoperative radiotherapy and consolidation chemotherapy afterwards, to achieve better outcomes. However, given the toxicity of radiotherapy and the safety of subsequent surgical resection, the choice and dose of chemotherapy in combination with this therapy are limited.

Second, preoperative radiotherapy for rectal cancer results in increased surgical complications and serious long-term toxicity. Although most studies have concluded that the short-term toxicity of preoperative radiotherapy for rectal cancer is tolerable, the surgical complications of radiotherapy, including anastomotic leak, poor perineal wound healing, and long-term toxicity, including bowel obstruction, frequent stools, fecal incontinence, sexual dysfunction, urinary incontinence, delayed cardiac events, hip fracture, and even induction of a second tumor, can cause serious harm. These toxicities would reduce patients’ compliance with subsequent adjuvant therapy. The toxicity of preoperative radiotherapy has received much attention in recent years, and several studies have consistently shown that patients treated with radiation have at least two to three times more severe toxicities that seriously affect the quality of life than those treated with surgery alone. For example, the incidence of unformed bowel incontinence was 49% and 15% for those treated with and without radiation therapy, respectively; erectile dysfunction was 35% and 11% for men, respectively; infertility was 100% and 2%, respectively; hip fracture was 5% and 1%, respectively; and second primary tumor was 9.5% and 4.3%, respectively.

Third, the indications for preoperative radiotherapy for rectal cancer are too broad. Previously, the criteria for patients receiving preoperative radiotherapy were locally advanced rectal cancer with tumors 10 cm or 12 cm inferior to the anus, i.e., T3, T4, and/or N1-2. However, the risk of local recurrence varies widely within this population. In fact, the risk of recurrence after radical surgery is much lower in patients with tumors located in the middle and upper rectal segments, or with no involvement of the mesenteric fascia, or negative lymph nodes (cT3N0M0) than in patients with tumors located in the lower rectal segment, or with invasion of the mesenteric fascia or even surrounding tissues, or positive lymph nodes (cT4bN+M0). The data from the Sun Yat-sen University cancer center that included 172 patients with low-risk rectal cancer with tumors 6-12 cm from the anus, clinical stage T3-4aN0M0, and no neoadjuvant therapy, showed that the 5-year local recurrence rate after TME was only 3.4%, and the 5-year recurrence-free survival rate (RFS) was 82.7%. If neoadjuvant radiotherapy is given to this group of patients as recommended by current guidelines, the benefit-risk ratio is clearly too low. Therefore, staging and risk stratification of rectal cancer based on location, level of invasion, infiltration of rectal mesenteric fascia and involvement of surrounding lymph nodes can be used to develop individualized treatment strategies to avoid excessive and harmful treatment, especially for preoperative radiotherapy. In recent years, the widespread use of high-resolution MRI has significantly improved the accuracy of preoperative staging of rectal cancer, thus making the above-mentioned staging and stratification possible. This concept is well illustrated in the newly published 2013 ESMO clinical guidelines for rectal cancer. The guidelines classify rectal cancer into very early, early (good prognosis), intermediate (poor prognosis) and advanced (very poor prognosis) stages. Early rectal cancer is defined as cT1-2 or mid-upper cT3a/b, N0 or upper cN1, with no involvement of the rectal mesenteric fascia (MRF-) and no extra-mural vascular infiltration (EMVI-). TME is recommended for these patients because of the better prognosis and lower local recurrence risk. The adjuvant radiotherapy and/or adjuvant chemotherapy would be considered if there are poor prognostic factors.

Finally, preoperative radiotherapy for rectal cancer reduces the patients’ compliance with subsequent adjuvant therapy. In fact, after neoadjuvant radiotherapy and surgical resection, patients' compliance with adjuvant chemotherapy is low. There are 27-35% of patients not receiving adjuvant chemotherapy and 50% unable to complete a full dose and course of adjuvant chemotherapy due to chemotherapy toxicity, surgical complications, and patient preference. If chemotherapy could be brought forward to the preoperative period, it would greatly improve patients’ tolerance and compliance, thus ensuring adequate doses and courses of perioperative chemotherapy.

For these reasons, for locally advanced rectal cancer with low local recurrence rate, neoadjuvant chemotherapy may be a better choice to control preoperative micrometastases and increase patients' compliance with perioperative chemotherapy and meanwhile avoid the toxicities of radiation. However, there are few studies on neoadjuvant chemotherapy for rectal cancer to date. Ishii Y's study enrolled 26 patients with resectable locally advanced rectal cancer (cT3/4N0-2M0) receiving two cycles of FOLFIRI chemotherapy (8 weeks in total) and achieved a pathological complete remission (pCR) rate of 7%, a 5-year RFS of 74% and a 5-year OS of 84%. The results of a later clinical study appear to be more encouraging. 32 patients with clinical stage II-III (non-T4) rectal cancer who were eligible for anus-preserving surgery were treated with 4 courses of FOLFOX + bevacizumab and 2 courses of FOLFOX chemotherapy. The result showed a pathologic complete remission rate of 27%, a 4-year recurrence-free survical rate of 84%, and an overall survival rates 91%. This study provides an supporting role for neoadjuvant treatment on rectal cancer. On the basis of this study, several studies in the United States, Japan, and China are currently exploring the feasibility of preoperative chemotherapy alone. However, these studies ignored the risk stratification of rectal cancer recurrence and enrolled the patients at high risk of recurrence (e.g., tumor invasion less than 1 mm from the circumferential margin and MRI staging of T3c-d). This indiscriminate inclusion of locally advanced rectal cancer is likely to bias the results of the study, thus significantly reducing the reliability of the study.

Therefore, we conduct a phase III randomized controlled clinical study to investigate the efficacy and safety of neoadjuvant chemotherapy alone (CAPOX) in patients with low-risk locally advanced rectal cancer. High-resolution MRI and ultrasound colonoscopy are used to define a cohort of low to medium risk locally advanced rectal cancer.

1. **Study Participating Institutions**

Sun Yat-sen University Cancer Center, Guangzhou, China;

Shantou Central Hospital, Shantou, China;

Yunnan Cancer Hospital, Kunming, China;

The First Affiliated Hospital of Nanjing Medical University, Nanjing, China;

Fujian Medical University Cancer Hospital, Fuzhou, China;

Meizhou People’s Hospital, Meizhou, China;

Liaoning cancer hospital, Shenyang, China;

Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China;

Guangdong provincial people’s hospital, Guangzhou, China;

Cancer Hospital of Shantou University Medical college, Shantou, China;

The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China;

Henan Cancer Hospital, Zhengzhou, China;

The First Affiliated Hospital of ChongQing Medical University, Chongqing, China;

First Affiliated hospital of Kunming Medical University, Kunming, China;

West China Hospital of Sichuan University, Chengdu, China;

Longyan First Hospital, Longyan, China;

Guangxi Medical University Cancer Center, Nanning, China;

Cancer Hospital of the University of Chinese Academy of Sciences, Hangzhou, China;

Hubei Cancer Hospital, Wuhan, China;

Jiangmen Central ospital, Jiangmen, China;

Shengjing Hospital of China Medical University, Shenyang, China.

21 centers in total.

1. **Objectives**

To compares neoadjuvant chemotherapy (nCT) with CAPOX alone to standard neoadjuvant chemoradiotherapy (nCRT) with Capecitabine for locally advanced rectal cancer (LARC) with uninvolved mesorectal fascia (MRF).

* 1. Primary Outcome Measure:

Local-regional failure-free survival

* 1. Secondary Outcome Measure:
     1. Disease free survival
     2. Pathologic complete response
     3. Tumor regression grade
     4. Pelvic R0 resection rate
     5. Overall survival
     6. Adverse event (AE) profiles
     7. Rates of receiving pre-operative or post-operative chemoradiation
     8. Post-operative complication
     9. Sphincter preservation rates
     10. Preventive diverting ileostomy rate
     11. Perioperative distant metastases rate
     12. Quality of Life

1. **Patient Eligibility**
   1. Registration – Inclusion Criteria
      1. Diagnosis of rectal adenocarcinoma
      2. Radiologically measurable or clinically evaluable disease
      3. Tumor located 5-12cm from anal verge. Protocol was revised to also enroll patients with tumor within 5 cm from anal verge from April 2019.
      4. Clinical stage T2N+ or T3-4aNany, M0 Clinical staging should be estimated based on the combination of the following assessments: physical examination by the primary surgeon, CT scan of the chest/abdomen/pelvis, and a pelvic MRI with or without an endorectal ultrasound (ERUS)
      5. No evidence that tumor is adjacent to (defined as within 1 mm) the mesorectal fascia on pre-operative MRI
      6. No tumor causing symptomatic bowel obstruction
      7. No distant metastasis
      8. ECOG performance status 0, 1
      9. White Blood Cell (WBC) ≥ 4,000/mm³
      10. Platelets ≥ 100,000/mm³
      11. Hemoglobin > 10.0 g/dL
      12. Total bilirubin ≤ 1.5 times upper limit of normal (ULN)
      13. AST and ALT ≤ 1.5 times ULN
      14. Creatinine ≤ 1.5 times ULN
      15. No co-morbidities or other concurrent disease that, in the judgment of the clinician obtaining informed consent, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens
   2. Registration – Exclusion Criteria
      1. Pregnant or nursing
      2. Patient of child-bearing potential not willing to employ adequate contraception
      3. Not willing to return to enrolling medical site for all study assessments
      4. With other invasive malignancy ≤ 5 years prior to registration; exceptions are colonic polyps, non-melanoma skin cancer, or carcinoma-in-situ of the cervix
      5. Chemotherapy within 5 years prior to registration (hormonal therapy is allowable if the disease-free interval is ≥ 5 years)
      6. Prior history of pelvic radiation
2. **Trial Design**
   1. Protocol summary and sample size

This clinical trial is a phase III randomized controlled trial designed to compares neoadjuvant chemotherapy (nCT) with CAPOX alone to standard neoadjuvant chemoradiotherapy (nCRT) with Capecitabine for LARC with uninvolved MRF. This trial includes 2 groups:

nCT group receive four cycles of CAPOX regimen followed by total mesorectal excision (TME) and 4 cycles of CAPOX.

nCRT group receive Capecitabine concurrently with radiation therapy followed by total mesorectal excision (TME) and 6 cycles of CAPOX.

study design

* 1. Sample size

On the basis of previous studies, assuming a 3-year local-regional failure-free survival of 93% for the nCRT group, with a non-inferiority margin of 1.6, a power of 80%, and a 2-sided alpha of 5%, an enrollment of 650 patients was planned.

* 1. Neoadjuvant chemotherapy

Patients receive four cycles of CAPOX regimen (Oxaliplatin 130 mg/m2 IV day 1 and Capecitabine 1000 mg/m2 twice daily for 14 days. Repeat every 3 weeks).

* 1. Neoadjuvant chemoradiotherapy

Patients receive Capecitabine 825 mg/m² twice daily administered orally and concurrently with radiation therapy for 5 days per week. The total dosage of radiotherapy was 50 Gy in 25 fractions to the gross tumor volume (GTV) and 45 Gy in 25 fractions to the clinical target volume (CTV) delivered by intensity-modulated radiation.

* 1. Details of radiation therapy
     1. Postural fixation: prone position, bladder filling, body fixation frame or vacuum bag fixation;
     2. CT scanning: Requires Acquisition of two sets of CT images in planar and enhanced time phases. Enhanced CT images can be omitted only for those who are allergic to contrast agent.
     3. Radiotherapy equipment: linear accelerator;
     4. Target area and irradiation field: the target area includes primary rectal focus and lymphatic drainage area. The treatment plan adopts IMRT or three-dimensional conformal radiotherapy design. The target area coverage and normal tissue limit are determined by the radiotherapy doctor according to the research results of ICRU report 50, ICRU report 62 and QUANTEC.
  2. Restaging after neoadjuvant therapy

Restaging assessments with pelvic MRI and EUS were performed 1 week following the completion of chemotherapy for nCT group and 5 weeks after the end of chemoradiotherapy for nCRT group. Patients with any evidence of local disease progression underwent chemoradiation as in the nCRT group before proceeding to surgery. In addition, patients with distant metastases were treated with current standard therapy. A watch-and-wait strategy was not routinely recommended for patients with clinical complete response (cCR). Watch-and-wait strategy was recommended only for patients who were candidates for abdominoperineal resection and achieved cCR.

* 1. Surgery

Patients without disease progression were scheduled for surgery with total mesorectal excision (TME) 2–4 weeks after chemotherapy for nCT group and 6–10 weeks after chemoradiotherapy for nCRT group. Performance of a preventive diverting ileostomy was at the discretion of the primary surgeon.

* 1. Adjuvant chemotherapy

CAPOX regimen (Oxaliplatin 130 mg/m2 IV day 1 and Capecitabine 1000 mg/m2 twice daily for 14 days. Repeat every 3 weeks) was started 3 weeks following surgery in both groups, regardless of pathological response stage. Patients in the nCT group received four cycles of CAPOX regimen, and patients in the nCRT group received six cycles of CAPOX regimen. Patients with postoperative pathologically confirmed positive margins were given adjuvant radiotherapy and chemotherapy.

* 1. Post-treatment surveillance

Post-treatment follow-up was done every 3 months for the first 2 years, and every 6 months for the next 3 years. Details of follow-up assessments, including CT scans or MRI, abdominal ultrasound，colonoscopy，carcinoembryonic antigen measurement, physical examination, and digital rectal examination, is provided in the protocol.

1. **Dose adjustment and treatment of adverse reactions**
   1. Hematological toxicity

Dose adjustment according to the lowest blood cell count after the last medication (see the following table):

|  |  |  |
| --- | --- | --- |
| Neutrophils (×109/L) | Platelet (×109/L) | The dose of next cycle |
| ≥ 0.5 | And ≥ 50 | No dose adjustment required |
| < 0.5 | Or < 50 | Subsequent doses of oxaliplatin and capecitabine should be reduced by 20% at the decision of the investigator |

After two times of dose reductions, if grade 4 neutropenia or grade 3-4 neutropenia with fever (>38.5℃) or grade 3-4 thrombocytopenia occur again, the third dose reduction is not required. The investigator will discuss whether to continue the treatment according to the specific situation.

* 1. Non-hematological toxicity

If grade 3-4 non-hematological toxicity (except vomiting and alopecia) such as diarrhea and mucositis occurred, the subsequent doses of oxaliplatin and capecitabine should be reduced by 20% at the decision of the investigator.

* 1. Hepatotoxicity

If the bilirubin is abnormal, the next cycle should be delayed. If it does not recover for more than 4 weeks, the treatment should be stopped. If the AST and/or ALT and/or alkaline phosphatase is abnormal, hepatoprotective treatment is possible for no more than 2 weeks. If it does not return to normal, the dosage can be adjusted according to the following table. If the liver function is restored in the next cycle, the dose should be increased to the previous level.

|  |  |  |
| --- | --- | --- |
| AST and/or ALT | Alkaline phosphatase | Dose adjustment |
| ＜1.5×ULN | ＜5×ULN | No dose adjustment required |
| ＞1.5×ULN and＜2.5×ULN | ＜2.5×ULN | No dose adjustment required |
| ＞2.5×ULN and＜5×ULN | ＜2.5×ULN | Subsequent doses of oxaliplatin and capecitabine should be reduced by 20-25% at the decision of the investigator |
| ＞1.5×ULN and＜5×ULN | ＞2.5×ULN and＜5×ULN |
| ＞5×ULN and/or＞5×ULN | | The delay is up to two weeks. If the patient still does not recover, it is up to the investigator to decide whether the patient should withdraw from the study. |

* 1. Peripheral neurotoxicity

If peripheral neurotoxicity of III-IV degree occurs, and the patient's life is severely affected, the investigator should discussed whether to reduce the oxaliplatin dose by 20% or discontinue the drug.

* 1. Treatment of adverse reactions

The treatment of adverse reactions can refer to the routine management principles of the trial center. When patients in nCT group (except those undergoing chemotherapy through the fourth cycle) are stopped for more than 4 weeks due to toxicity, the patients should be transferred to group B and receive preoperative radiotherapy and chemotherapy.

1. **Clinical safety assessment**
   1. Definition
      1. Adverse event (or adverse experience, AE)

Refers to any adverse medical event that occurs in a subject or clinical subject, which is not necessarily causally related to treatment. Therefore, AEs can be any abnormal or unintended signs (such as: abnormal laboratory results), symptoms, or transient drug-related diseases, and consideration should be given to whether it is related to medication. According to management needs, adverse events that occur before and after treatment are regarded as adverse events. Therefore, safety monitoring (reporting of adverse events or serious adverse events) should be carried out from the beginning of the subjects' enrollment to the end of the study. Adverse events that occur during the signing of the informed consent form and the start of the study treatment are also considered AEs.

* + 1. Adverse Drug Reaction

All toxic and unintentional reactions to the drug related to any dose should be considered Adverse Drug Reactions (ADRs). The reaction to the drug means that the causal relationship between the drug and the AE is at least reasonably possible, which means that this relationship cannot be excluded.

* + 1. Serious Adverse Event

Serious adverse event (SAE) was defined as any event that results in death, life-threatening, hospitalization (initial or prolonged), congenital anomaly, birth defect, disability or permanent damage, and other important medical events affecting the safety of the participants.

* 1. The record and evaluation methods of AE

All AEs should be recorded in the corresponding section of the CRF. In addition, the SAE report form (including initial or follow-up report) should be completed.

* + 1. Recording of each event
       1. Describe the AE in medical terms, not as a report of the subject;
       2. Date of occurrence (start date);
       3. Time of occurrence (start time);
       4. Date of recovery (End date);
       5. Recovery time (end time).
    2. Classification

The researcher shall perform the evaluation and classification according to the definition of NCI-CTC version 4.0. Level 1 = mild; Level 2 = moderate; Level 3 = severe; Level 4 = life threatening or disabling; Level 5 = death.

A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: <http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm>

* + 1. The relationship between AE and drugs

The investigator should evaluate the causal relationship between the adverse event and the study drug; the decisive factor evaluated in the record is the time correlation between the AE and the study drug. The causal relationship between the adverse event and the study drug or research protocol is judged as follows:

* + - 1. Definite

There is a reasonable causal relationship between the AE and the study drug. Discontinuation of the drug has an impact on the response, and when clinically feasible, it will occur if the drug is re-administered.

* + - 1. Probable

There is a reasonable causal relationship between the AE and the study drug. Discontinuation (withdrawal of the drug from the study) has an impact on the response. There is no need to re-dose to prove it.

* + - 1. Possible

There is a reasonable causal relationship between the AE and the study drug. Lack of discontinuation information (withdrawal information) or not yet clear.

* + - 1. Unlikely

There is a temporal relationship with the study drug, but there is no reasonable causal relationship between the AE and the study drug.

* + - 1. Unrelated

There is no temporal relationship with the study drug (too early, too late, or no medication), or there is a reasonable causal relationship between the AE and another drug, concomitant disease or environment.

* + 1. Treatment outcome

Define the treatment outcome of measures taken for the treatment of this study (none, suspending treatment, reducing dose, delaying treatment, slowing down the speed of intravenous infusion) and other measures (none, combined medication, requiring hospitalization or prolonging hospitalization, performing surgery, delaying chemotherapy, discontinuing chemotherapy, chemotherapy reduction) as follow: cured with sequelae, cured without sequelae, not cured no treatment needed, not cured but need treatment, and death.

* 1. Reporting procedure for serious adverse events

In case of any serious or clinically significant adverse event or laboratory abnormal test value during the study period, regardless of the treatment received by the subject, the researcher is obliged to report each serious adverse event to the adverse drug reaction monitoring center, the study sponsor and the ethics committee by telephone, fax or e-mail within 24 hours. After the telephone report, the written information needs to be sent by fax. The report shall provide the information of the reporter and receiver, including name, address, telephone and fax number, and indicate that the report is a "preliminary" report or a "follow-up" report. If necessary, the report form shall be attached with the relevant medical record report form. The investigator shall ensure that the public ethics committee or the competent authority is provided with any additional required information on the subject's death. It notable that all forms must be dated and signed by the investigator, or by an authorized colleague of the investigator. For special problems, please contact the contact person of the principal investigator in time.

* 1. Monitoring of adverse events

Any adverse events during the study were monitored and followed up until the end of the study. In addition, SAEs must be reported through the SAE form.

* 1. The evaluation of the laboratory index

All laboratories conducting clinical evaluation in the hospital shall comply with the basic principles of good laboratory practice (GLP) and the requirements of their hospital.

* 1. Clinical safety assessment

NCI-CTC AE version 4.0 will be used to evaluate the clinical safety of treatment in the study. The adverse events of the subjects must be evaluated at each clinical visit.

1. **Outcome Measures**
   1. Evaluation of local recurrence or metastasis

When clinical symptoms (anal pain, blood in the stool, lower extremity edema, etc.) appear, or CEA is progressively elevated, or suspicious signs appear in chest or abdominal imaging, further examination is needed to find local recurrence or progression of disease metastasis. Local regional recurrence mainly refers to the recurrence of tumors in the local area of the operation or nearby organs. Distant metastasis refers to the recurrence of tumors outside the above-mentioned areas. Disease-free survival means that the patient has not found tumor recurrence or the occurrence of new colorectal cancer through systematic evaluation.

The diagnosis of clinical recurrence and metastasis must meet at least one of the following: 1. Radiological indication of recurrence (ultrasound, CT, MRI, PET-CT); 2. Positive cytological biopsy (appearance of ascites, recurrence of anastomosis, suspicious imaging findings).

The recurrence date refers to the date when the recurrence was found using the above-mentioned diagnostic methods. When a recurrence occurs, the researcher should indicate the location of the recurrence and the diagnostic method used. When clear imaging evidence cannot be obtained, a positive result of cytology or biopsy should be obtained. Elevated CEA alone cannot be used as evidence of local recurrence or metastasis of rectal cancer.

* 1. Calculation of time
     1. Local-regional failure-free survival is defined as the time interval between the date of randomization and the date of local or regional progression/relapse, or death, whichever occurred first.
     2. Disease-free survival is defined as the time interval between the date of randomization and the date of the first cancer-related event, second cancer, or death from any cause, whichever occurred first.
     3. Overall survival is defined as the time interval between the date of randomization to the date of death. If the patient has been alive, the time until the last follow-up is taken as the overall survival period.
     4. Tumor assessment (abdomen and pelvis CT/MRI or ultrasound and chest CT) and CEA must be performed every 6 or 12 months after randomization, or when the patient shows signs of progression (ie, clinical signs appear). Suspicious lesions detected by ultrasound must be confirmed by CT/MRI. All re-operations or further anti-cancer treatments should also be recorded. If a confirmed recurrence of colorectal cancer or new colorectal cancer occurs during the treatment period, the patient will withdraw from the follow-up. All patients should be followed for at least 5 years. If a biopsy is done, a biopsy report should be provided.
  2. Pathological Complete Response (pCR)

Pathological response will be made based on assessment of the surgical specimen at the primary treatment site. This assessment is made in addition to the AJCC 7th edition summary staging. A pCR must include no gross or microscopic tumor identified anywhere within the surgical specimen. This must include:

• No evidence of malignant cells in the primary tumor specimen

• No lymph nodes that contain tumor.

* 1. Tumor Regression Grade

The definition of a non-pCR will include any surgical specimen that has any evidence of residual tumor manifest in the primary or regional lymph nodes. For patients who do not meet criteria for a pCR, the extent of response to preoperative therapy will be graded using the Tumor Regression Grade (TRG) schema that is included in the AJCC 7th edition. This was also used by Rodel in the pre/postoperative rectal cancer study and was subsequently adopted by the AJCC [Rodel (JCO 2005; 23:8688-8696)]. This schema evaluates the degree to which the primary rectal tumor specimen has responded to neoadjuvant treatment.

|  |  |  |
| --- | --- | --- |
| Tumor Regression Coding Based on AJCC 7th Edition | | |
| TRG | Response Categorization | Description |
| TRG-0 | Complete | No viable cancer cells |
| TRG-1 | Moderate | Single cells or small groups of cancer cells |
| TRG-2 | Minimal | Residual cancer outgrown by fibrosis |
| TRG-3 | Poor | Minimal or no tumor kill; extensive residual cancer |

* 1. Resection limits
     1. R0 resection: All gross disease has been removed, and microscopic examination reveals all surgical margins free of tumor.
     2. R1 resection: There is evidence of tumor manifest at 1 or more surgical resection margins based on microscopic pathologic assessment of the tumor specimen but there is no macroscopic evidence of tumor at any resection margin nor is there macroscopic evidence of residual tumor based on the surgeon's operative report.
     3. R2 resection: The surgical pathologist identifies any macroscopic evidence of tumor at any of the surgical resection margins or there is macroscopic evidence of residual tumor based on the surgeon's operative records.
     4. Patients with postoperative pathologically confirmed positive margins were given adjuvant radiotherapy and chemotherapy.
  2. Evaluation of toxicities

The severity of AE and the laboratory findings were graded by the investigators according to Common Terminology Criteria for Adverse Events, version 4. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: <http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm>

The maximum grade for each type of adverse events during neoadjuvant chemotherapy and chemoradiation therapy, and surgical complications will be recorded for each patient.

Follow-up for patient safety should be done during the treatment period and 30 days after the end of the last cycle. The reason for the delay or interruption should be recorded on the CRF form.

* 1. Evaluation of the efficacy

Overall efficacy are evaluated according to RECIST criteria. After completing the neoadjuvant treatment, the patient must receive the same evaluation in the same center. Lesions are measured according to RECIST criteria.

Complete remission (CR): All target lesions disappear; the short diameters of all pathological lymph nodes (including target nodules and non-target nodules) must be reduced to <10mm.

Partial remission (PR): The sum of the target lesion diameters is reduced by at least 30% relative to the baseline level.

Progression of disease (PD): When the minimum sum of all target lesion diameters measured throughout the study process is used as a reference, the sum of diameters relatively increases by at least 20% (if baseline measurement is the minimum, then the baseline value is used as the reference); in addition, the requirement that the absolute sum of diameters increases by at least 5mm must be met (the appearance of 1 or multiple new lesions is also considered to be PD).

Stable disease (SD): The decrease of target lesion has not reached PR and the increase of target lesion has not reached PD, but rather falling between these 2 indexes; the minimum sum of diameters can be used as a reference during the study.

1. **Random Assignment and Masking**

This research is an open-label research. According to the preoperative lymph node status and tumor locations, a stratified randomized block design was adopted to randomly assign patients to one of the two treatment groups. It is an open study, so there is no blinded treatment allocation. Random numbers are assigned according to the order in which patients joined the study. In the study, all patients have unique numbers. Only randomization of patients by qualified investigators will be accepted.

A list of questions must be answered during randomization, which is also part of the report. These questions should be completed by the investigator before randomization is achieved. The following items are included: trial code, unit code, name of the contact person, name of centeral principal, name of the patients(up to 4 letters), chart number of patient (if available) ,and patient’s birthday (day/month/year). All selection criteria will be checked. Finally, the randomization process will give the patient a number (as his identification code). This number must be recorded in the randomization directory along with the randomization data. The completed directory should be signed by the investigator and sent to the data center together with the initial patient data. The identification code obtained by the patient after randomization should be marked on all report forms.

1. **Statistical Analysis**
   1. Analysis method

Concerning the statistical description, the counting data adopt the rate, the measurement data adopt the mean and 95% confidence interval. When comparing the two groups, categorical variables are compared using the χ2 or Fisher's exact test, and continuous variables are compared using the t-test. Kaplan-Meier and Log Rank methods are used for survival analysis, and Cox proportional hazards model is used for prognosis analysis. A two-sided P value < 0.05 is considered to indicate statistical significance. All statistical analyses were performed using SPSS version 24.0 (SPSS, Chicago, IL).

* 1. Analysis populations

Before locking the database, determine the patient groups contained in the following three data sets.The primary efficacy analysis will be conducted in Modified Intent-to-treat (mITT) populations and per-protocol (PP) populations. Secondary efficacy analysis and exploratory analysis will be conducted in the mITT populations. Non inferiority analysis will be conducted in the PP populations.

* + 1. The mITT population includes all randomized subjects who met all inclusion/exclusion criteria, applied at least one dose of assigned neoadjuvant therapy. The analysis will be carried out according to the treatment group randomly assigned by the patients.
    2. The PP population includes all randomized subjects who met all inclusion/exclusion criteria, completed the assigned neoadjuvant therapy without major protocol deviations. The analysis will be carried out according to the treatment group randomly assigned by the patients.
    3. The safety population includes all randomized subjects who received study treatment. The safety population is used to analyze all safety parameters. The analysis will be carried out according to the drugs they actually received.
  1. Interim Analysis

No interim analysis of efficacy endpoints was performed in this study. An independent data security monitoring team will monitor security data throughout the study. Descriptive analysis of all safety data will be performed after all patients selected for this study have completed study treatment. This analysis will be strictly limited to safety data and does not include any efficacy endpoints.

1. **Schedule of the trial**
   1. Before treatment

All patients participating in this trial should sign an informed consent form and get a copy of the informed consent form. If the patient agrees to participate, they should fill out the participation form immediately and sign. Within 14 days before randomization, the investigator should evaluate the following clinical and laboratory indicators in detail.

* + 1. Past history, including: age, gender, tumor location, disease stage, histological stage, whether there is a history of perforation or obstruction, the time of surgery, and the procedure.
    2. ECOG performance status (refer to the following table)

|  |  |
| --- | --- |
| Grade | ECOG performance status |
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours |
| 3 | Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot carry on any selfcare; totally confined to bed or chair |

* + 1. Clinical examination, including weight and height.
    2. Electrocardiogram
    3. Collect clinical laboratory data

Hematological indicators such as hemoglobin, white blood cells, platelets, and neutrophils. Non-hematological indicators: creatinine, alkaline phosphatase, and total bilirubin.

* + 1. Carcinoembryonic antigen (CEA)
    2. Pathological diagnosis of tumor (primary cancer), including staging and grading.
    3. CT with contrast (chest/abdomen)
    4. MRI or ERUS of the pelvis (MRI preferred)
  1. During treatment

The safety assessment should continue until 30 days after the last chemotherapy.

The test plan is as follows:

* + 1. Nervous system examination: before each cycle of chemotherapy.
    2. Hematology (hemoglobin, white blood cells, platelets and neutrophils): before each cycle of chemotherapy.
    3. Chemistry (Alkaline phosphatase, total bilirubin, glutathione and aspartate aminotransferase, creatinine): before each cycle of chemotherapy.
    4. Toxicity/side effects: Before each cycle of chemotherapy, until 30 days after the end of chemotherapy or other treatment-related toxicity events.
    5. CEA: Every 3 months.
    6. Abdominal and pelvic CT scan or MRI: before surgery, or to determine whether there is a recurrence (increased CEA, symptoms, abnormal ultrasound findings, etc.).
  1. After treatment

After the treatment, follow-up should be done according to the items and time in the following table until tumor recurrence or at least 5 years. If recurrence is suspected, CT of the pelvic and abdominal cavity or chest should be performed, and PET/CT should be performed if necessary. If lesions are found in colonoscopy, the period of colonoscopy can be shortened according to the specific situation.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Project | Postoperative time (month) | | | | | | | | | | | | | | |
| 1 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 30 | 36 | 42 | 48 | 54 | 60 |
| Symptom | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Physical examination | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Blood routine | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| CEA | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Abdominal CT scan or MRI |  |  |  |  | √ |  |  |  | √ |  | √ |  | √ |  | √ |
| Abdominal ultrasound |  | √ | √ | √ |  | √ | √ | √ |  | √ |  | √ |  | √ |  |
| Pelvic MRI |  |  |  |  | √ |  |  |  | √ |  | √ |  | √ |  | √ |
| Chest X-ray |  |  | √ |  |  |  | √ |  |  | √ |  | √ |  | √ |  |
| Chest CT |  |  |  |  | √ |  |  |  | √ |  | √ |  | √ |  | √ |
| Colonoscopy |  |  |  |  | √ |  |  |  |  |  | √ |  |  |  | √ |
| QOL Assessment | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Efficancy evaluation | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |

1. **Data collection**

All information should be recorded in a timely, truthful and detailed case report form (CRF) or CRF software. The medical record form should be filled out by a person appointed by each participating unit and signed by the person in charge of the project in each unit before it can be regarded as a valid case. The responsible unit will regularly send personnel to each unit to check and collect the CRF with the cooperating unit, and submit it to the clinical trial management center of the hospital for filing once every six months.

After the clinical trial is finish, each participating research unit will write a summary of the clinical scores of each unit in accordance with the requirements of the clinical summary specifications. The clinical research lead unit summarizes and organizes all the tables, and writes a general clinical summary report in accordance with the specifications.

1. **Collection of blood and tissue samples**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Specimen type | Paraffin embedding | Fresh specimen (DNA extraction) | Before neoadjuvant therapy | After two cycles of nCT or after nCRT | Before operation | Before adjuvant therapy | After adjuvant therapy |
| Biopsy specimens before treatment | X | X |  |  |  |  |  |
| Surgical resection of tissue specimens | X | X |  |  |  |  |  |
| blood sample (10ml) |  |  | X | X | X | X | X |

1. **Ethics and informed consent**
   1. Ethical requirements

The trial is carried out in accordance with the Declaration of Helsinki and International Harmonization Conference Good Clinical Practice guidelines. The protocol is approved by the central ethics committee of Sun Yat-sen University Cancer Center (Guangzhou, China), and local ethics committees of all participating hospitals.

* 1. Informed consent

The investigator or the person designated by the investigator has the responsibility (if allowed by local regulations) to obtain the written informed consent of each subject participating in the study by correctly explaining the purpose, method, expected benefits and potential hazards of the study.

For subjects who are unqualified or unable to sign the legal consent, their legal representative must sign the informed consent. If the subject and his legal representative can not read, a notary should be present during the discussion of informed consent. After the subjects and their representatives orally agree to participate in the test, the witness shall sign the informed consent form to prove that the contents of the agreement have been accurately explained and understood. The investigator or designee shall also explain that the subject may refuse to participate in the study or withdraw from the study early for any reason at any time. The CRF of this study includes a section recording the subject's informed consent, which should be filled in accurately. If the emergence of new safety information leads to significant changes in hazard / benefit evaluation, the informed consent form shall be reviewed or updated as needed. All subjects (including those who have started treatment) should be informed of the new information, an updated informed consent form should be handed over to the subjects, and their consent should be obtained to continue the study.

1. **Quality Control**

The standard operating procedures is established for the quality control of the clinical trial, which can ensure the timely and accurate review of the implementation of the clinical trial, and improve the quality of the clinical trial.

* 1. Consistency quality control between research centers
     1. Determine unified MRI parameters, staging criteria and pathological complete remission criteria;
     2. Before the study, the lead unit shall organize relevant personnel, especially the heads of imaging department, ultrasound department, pathology department and sub centers and research assistants for unified training;
     3. Each center is divided into stages independently by two imaging experts. If the results are inconsistent, the data shall be submitted to the evaluation team of the center for judgment;
     4. Every six months, the center's image evaluation team evaluates the image data of each center and gives feedback on improvement suggestions.
     5. Other quality control measures
* The research scheme is jointly formulated by the units participating in the research, and the statistical experts participate in the whole process.
* Formulate various SOPs for the study (including concomitant medication standards, adverse reaction monitoring and treatment plan).
* Establish standardized evaluation methods (various diagnostic and curative effect judgment criteria, etc.).
* Designate quality control personnel and formulate quality control plan and regular inspection.
* Establish a coordination committee, a follow-up team, and a data and safety monitoring committee. The members of the Safety MMonitoring Committee are as follows: biostatistician (Qing Liu), clinical trial methodology expert (Su-Mei Cao), bioethics expert (Qiong Chen), and trial manager (Yang Zhang).
  1. Data quality control

The data is sent to the center and managed by a dedicated person. A special database is established for corresponding inspection and evaluation according to requirements, and recorded in the CRF table. All forms must be completed, signed and dated by the person filling in. Research supervisors supervise and urge the completion of the CRF form every three months, and review and sign it. All items should have corresponding objective basis for review.

Participating units should complete each link of the research according to the specific requirements. If it is not completed, be sure to indicate the reason. Before the start of the experiment, the heads of the units and researchers participating in this research study the general principles of GCP and discuss the research plan in order to fully understand and master the requirements and contents of this research. Principal investigator and researchers of each unit should ensure the quality of their research, strictly control the inclusion and exclusion criteria, and carefully fill in the CRF. If any mistakes happen and need correction, it shall be signed and dated, and the original amendment can be identified. The investigator of each unit should carefully check each CRF and sign it after confirming that it is complete and correct. The medical records required to be recorded are true and reliable, and accept random checks at any time.

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