BMJ Open

Dose escalation of preoperative short-course radiotherapy followed by neoadjuvant chemotherapy in locally advanced rectal cancer: protocol for an open-label, single-centre, phase I clinical trial

Meng-xia Zhang,[1] Xiao-bo Li,[1,2] Bing-jie Guan,[1] Guo-xian Guan,[3] Xiao-yan Lin,[4] Xiao-dong Wu,[5,6] Pan Chi,[3] Ben-hua Xu[1,7]

To cite: Zhang M, Li X, Guan B, *et al*. Dose escalation of preoperative short-course radiotherapy followed by neoadjuvant chemotherapy in locally advanced rectal cancer: protocol for an open-label, single-centre, phase I clinical trial. *BMJ Open* 2019;**9**:e025944. doi:10.1136/bmjopen-2018-025944

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-025944).

Received 16 August 2018
Revised 26 January 2019
Accepted 29 January 2019

For numbered affiliations see end of article.

Correspondence to
Dr Xiao-bo Li; lxbclf@126.com, Professor Pan Chi; panchi198908@sina.com and Professor Ben-hua Xu; benhuaxu@163.com

ABSTRACT

Introduction Preoperative radiotherapy followed by total mesorectal excision with adjuvant chemotherapy has been recommended as the preferred treatment method for locally advanced rectal cancer (LARC). Similar rates of local control, survival and toxicity were observed in preoperative long-course chemoradiotherapy (LCRT) (45–50.4 Gy in 25–28 fractions) and in short-course radiotherapy (SCRT) with 25 Gy over five fractions. Both regimens lower the local recurrence rates compared with that of surgery followed by postoperative radiotherapy. With the simplicity and lower cost of SCRT, a growing number of patients have been receiving SCRT as preoperative radiotherapy. However, the currently established SCRT (25 Gy over five fractions) followed immediately by surgery resulted in poor downstaging and sphincter preservation rate. The pathological complete response (pCR) rate is also markedly lower with SCRT than with LCRT (0.7%vs16%). Several studies recommended SCRT with delayed surgery for more than 4 weeks with expectation of improved pathological outcomes and fewer postoperative complications. While a number of clinical trials demonstrated a persistently better overall local control with SCRT than with LCRT, overall survival advantage has not been observed. Since survival is mainly depended on distant metastases, efforts should be made towards more effective pathological response and systemic treatment. Given the apparent advantages of SCRT, we aimed to establish a dose escalation of SCRT and sequential modified FOLFOX6 (mFOLFOX6) as preoperative therapy for LARC with objectives of achieving an optimal balance of safety, cost effectiveness and clinical outcome, and to support further investigation of this regimen in a phase II/III setting.

Methods In this phase I study, three dose levels (6Gy×5F, 7Gy×5F, 8Gy×5F to gross tumour volume, while keeping the rest of irradiated volume at 5Gy×5) of SCRT followed by four cycles of mFOLFOX6 chemotherapy as neoadjuvant therapy will be tested by using the traditional 3+3 design. The pCR rate, R0 resection rate, sphincter preservation rate and treatment related toxicity will be assessed.

Ethics and dissemination The study protocol was approved by the Ethics Committee of Fujian Medical University Union Hospital (No. 2017YF020-02) and all participants provided written informed consent. Results from our study will be disseminated in international peer-reviewed journals. All study procedures were developed in order to assure data protection and confidentiality.

Trial registration number NCT03466424; Pre-results.

Strengths and limitations of this study

- This protocol describes a phase I study with novel concept and design.
- Dose escalation of preoperative short-course radiotherapy (SCRT) followed by mFOLFOX6 chemotherapy will be conducted according to the traditional 3+3 design.
- The main advantage of the traditional 3+3 design is that it is easy to implement and safe.
- Our study is expected to lay the foundation for conducting future phase II/III clinical trials that may transform the preoperative treatment paradigm of SCRT from conventional 5×5 Gy to 5×6 Gy, 5×7 Gy or 5×8 Gy followed by mFOLFOX6 chemotherapy for patients with locally advanced rectal cancer.
- This phase I study design with relatively small sample size does not allow for accurate outcomes analysis.

BACKGROUND

Rectal cancer is one of the most common malignant tumours in western countries and its incidence and mortality rates have been ascending for several decades in China. According to statistics, the incidence of colorectal cancer had increased to 13% in 2015 compared with only 7% in 2002 in China. In the distribution of urban and rural

areas, both morbidity and mortality were much higher in urban areas than in rural areas (69.93% vs 30.07% and 66.25% vs 33.75%, respectively).[1–3] Surgical resection is the primary treatment method for resectable rectal cancer. Postoperative chemoradiotherapy improves local control but also lowers the tolerance rate and increases the incidence of postoperative complications. It is generally not recommended as a regular treatment strategy excepting patients who have high risk of recurrence after surgery. Preoperative chemoradiotherapy followed by total mesorectal excision and adjuvant chemotherapy has been recommended as the preferred regimen for locally advanced rectal cancer (LARC) with more effectiveness in local control compared with postoperative radiotherapy.[4 5] The traditional long-course chemoradiotherapy (LCRT) is 45–50.4 Gy in 25–28 daily fractions given with concurrent chemotherapy and delayed surgery (4–8 weeks after chemoradiotherapy). Also considered an alternative treatment option is preoperative short-course radiotherapy (SCRT) of 25 Gy in five daily fractions and followed by immediate surgery (1 week after SCRT). Similar rates of local control, survival and toxicity were observed in these two regimens.[6 7] Although SCRT reduce treatment interval and cut-down costs, its pathological complete response (pCR) rates are relatively low. Bujko *et al* reported that the pCR rates for SCRT and LCRT are 0.7% and 16%, respectively.[6] This difference may be partially related to the interval between preoperative radiotherapy and surgery. The pCR rates are higher in patients who have the longer interval.[8] In the latest multicentre, randomised, non-blinded, phase III, non-inferiority clinical trial (Stockholm III), participants were randomly assigned to receive either 5×5 Gy radiation dose followed by immediate surgery within 1 week (SCRT) or after 4–8 weeks (SCRT with delay) or 25×2 Gy radiation dose followed by surgery after 4–8 weeks (LCRT with delay). All these regimens show similar oncological results. However, LCRT with delayed surgery prolongs the treatment interval substantially. Although radiation-induced toxicity was observed in SCRT with delayed surgery, postoperative complications were significantly reduced compared with SCRT followed by immediate surgery. Thus, SCRT with delayed surgery was recommended as a useful alternative to conventional SCRT with immediate surgery.[9]

The optimal pattern of dose fractionation of preoperative radiotherapy is still indicated for further exploration. J Widder *et al* reported that SCRT of 25 Gy administered in 2.5 Gy two times per day within 1 week for resectable rectal cancer generated a well-tolerated and simpler way to increase local control.[10] A prospective phase II study of SCRT of 2.9 Gy twice daily fractions to a total dose of 29 Gy also resulted in tolerable toxicity and favourable local control.[11] Although both modifications of SCRT have resulted in acceptable toxicity and good local control, the overall survival remains statistically unchanged. Besides, accelerated irradiation (two times per day) increases daily workload. A prospective phase II study made a boost to the gross tumour volume (GTV) up to a total of 30 Gy in five fractions to investigate the feasibility and the impact on pCR rates. This trial achieved a pCR rate of 16% with acceptable toxicity.[12] This suggests the potential benefit of achieving better local control, even the overall survival by increasing the fractional dose to the GTV. Hence, we proposed the dose escalation trial of boosting GTV from 5×6 Gy, 5×7 Gy to 5×8 Gy in SCRT for treating LARC. The theoretical basis lies in:

To improve the tumour killing

Biological equivalent doses (BED) were used for comparison of various fractionations of radiotherapy. Taking into account the cell proliferation, BED can be calculated by:
BED (Gy)=nd × [1 + (d /α / β)] − γ /α(T − Tk) n: number of fractions d: single fractional dose (Gy)
α / β: 10 Gy for rectal tumour, 3 Gy for normal tissues
γ / α: a daily repair rate, set as 0.6 Gy for rectal tumour
T: overall treatment time
Tk: a proliferation delay, set as 7 day for rectal tumour cells.
If T<Tk, the proliferation term is disregarded. For normal tissue, the proliferation term is also disregarded.

Taking tumour proliferation into account, the above BED formula arrives at a same BED of 37.5 Gy for both 1.8Gy ×25 and 5 Gy ×5, suggesting the same cell killing effect. However the lower pCR rate of SCRT implies a lesser effective tumour killing. This might be attributed to factors such as tumour reoxygenation and/or the presence/absence of chemotherapy. Without increasing the toxicity such as importantly sphincter dysfunction, the logical step toward higher therapeutic effect is then naturally to escalate the GTV dose and/or adding concurrent or sequential chemotherapy, leaving the rest of the irradiated volume at the established 5 Gy ×5. In this proposed trial, we will re-evaluate the published result of GTV boost of 6 Gy ×5 and further explore the toxicity and clinical efficacy of GTV dose escalation with sequential chemotherapy for SCRT.

To induce tumour immune response

Several studies reported that radiotherapy can induce or regulate immune response, which can suppress tumour growth and generate inflammatory response. Radiotherapy can stimulate tumour therapeutic effects in both local-regional (within radiation field) and distant area of body.[13 14] Surace *et al* found that tumour cell death and transient activation of complement can be induced by radiotherapy to produce proinflammatory anaphylatoxin C3a and C5a. These proinflammatory anaphylatoxin are essential in tumour response to radiotherapy and tumour-specific immune stimulation.[15] Lee *et al* found that immune responses could be inhibited by exhausting lymphocytes when received conventional radiotherapy (2 Gy daily fraction).[16] On the contrary, high dose of radiation can enhance the immune response. Compared with 2 Gy daily fraction, ablative radiotherapy of a single dose of up to 20 Gy could result in more apoptosis, necrosis

and senescent cells.[17] The underlining mechanism may involve cell surface molecular components, the release of soluble medium and signal transduction.[18] Results from Parker JJ's study demonstrated that tumour cells undergo immunogenic deaths following high dose irradiation through the transformation in phosphorylation of NF-κB family.[19]

It has been well established that preoperative chemotherapy plays a crucial role in eliminating potential micrometastases. A multicentre, phase III study (Polish II) enrolled 515 patients with fixed cT3 or cT4 rectal cancer to receive either SCRT followed by three cycles FOLFOX4 or LCRT. They found that patients received SCRT and FOLFOX4 had lower acute toxicity (p=0.006), higher R0 resection rates (77% vs 71%, p=0.07) and higher value of pCR rates (16% vs 12%, p=0.17).[20] Another phase II study enrolled 76 patients with cT3-4 rectal cancer to receive SCRT and four cycles mFOLFOX6 sequential chemotherapy. The pCR rate reached 25% and T-down-staging rate achieved up to 71%.[21] It is worth noting that when adding preoperative chemotherapy, the prolonged interval between SCRT and surgery did not incur the complication by the radiation-fibrosis as commonly anticipated. Therefore, we hypothesise that SCRT with dose escalation to GTV followed by mFOLFOX chemotherapy as preoperative treatment method is safe and may further improve the treatment outcome for patients with LARC. The advantages of this therapy regimen include:

1. Not only does escalation of fractional dose of SCRT increase the BED, it may lead to radiation-induced immune response and result in enhanced therapeutic control of both local recurrence and distal metastasis.
2. The prolonged interval between preoperative radiotherapy and surgery, adding chemotherapy in between will allow the antitumour effects of radiotherapy and chemotherapy to fully take place and to achieve higher pCR rates and R0 resection rates.
3. Implementation of standard mFOLFOX6 chemotherapy can be synergetic with radiotherapy to potentially eliminate micrometastases and control the primary tumours.

METHODS

Study design

This trial is a phase I single-centre, hospital-based, dose-escalation, observational study in Fujian Medical University Union Hospital. Briefly, patients with LARC (T3-4 and/or N+) and meet the other inclusion criteria will be enrolled to receive SCRT in three radiation dose levels (5×6 Gy, 5×7 Gy, 5×8 Gy) according to the time-lapse series. Four cycles of mFOLFOX6 chemotherapy will be implemented to patients 1 week later after completing SCRT. Two weeks after the completion of chemotherapy, patients will be transferred to general surgery department to receive surgery. Outcomes measure will be conducted within 4 weeks after surgery (figure 1). Patients are currently being recruited and enrolled; the first patient was enrolled in June 2018. We used the SPIRIT checklist when writing our report.[22]

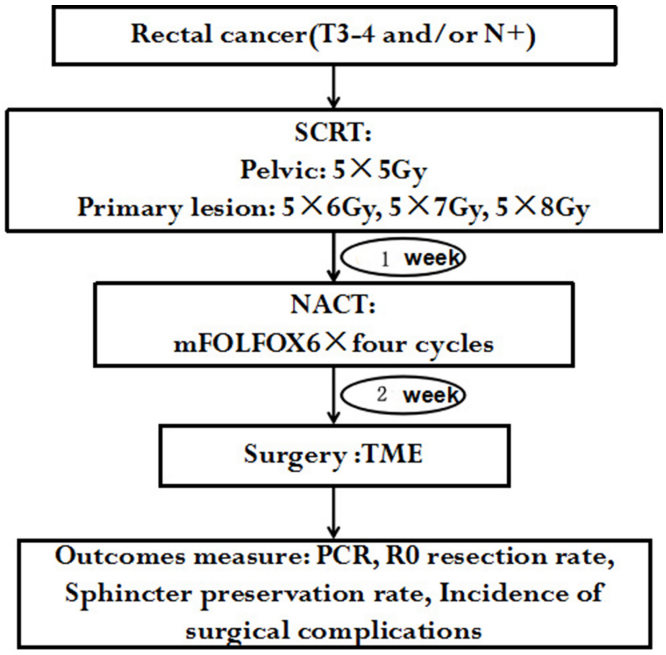

Figure 1 Study flowchart. NACT, neoadjuvant chemotherapy; PCR, pathological complete response; SCRT, short course radiotherapy; TME, total mesorectal excision.

Patient and public involvement

Patients and or public were not involved in this study.

Treatment methods

Short-course radiotherapy

The SCRT technique has been well described in many published literatures.[23–25] To sum up, all patients shall undergo a contrasted CT simulation of the pelvis and lower abdomen with 5 mm slice thickness in a supine position. Oral contrast shall be given 30 min prior to simulation in order to differentiate the small bowel from the large bowel. The CT images are then transferred to the treatment planning system for contouring the target volume and organs at risk (OARs) and planning. The GTV shall be contoured based on clinical information, including digital rectal examination, endoscopy ultrasound and MRI. The clinical target volume (CTV) shall include a minimum of a 3 cm craniocaudal margin to the GTV in addition to the entire mesorectum, presacral and internal iliac lymph node drainage regions. Planning target volumes (PTVs) for GTV and CTV shall be delineated with an additional 1 cm margin separately. Critical normal structures including the small bowel, bladder, femoral head, femoral neck and pelvic bones (including sacrum, ilium, pubis and ischium) shall be contoured according to the pelvic normal tissue contouring guidelines of Radiation Therapy Oncology Group (RTOG).[26] The dose prescribed to PTV-GTV will be 30-40 Gy per five fractions and to PTV-CTV, 25 Gy five fractions. The doses to OARs shall be limited as follows: V45 <35% for

bladder, V30 <15% for femoral head and V30 <60% and Dmax <45 Gy for small bowel. All patients were irradiated with one fraction daily for five consecutive days in 1 week. The prescription dose must cover at least 95 % volume of the PTVs.

Sequential chemotherapy

For preoperative chemotherapy following SCRT, mFOLFOX6 regimen is to be given as follows:

- oxaliplatin: 85 mg/m2 intravenously for 2 hours on day 1;
- leucovorin calcium: 400 mg/m^2 intravenously 2 hours before fluorouracil on day 1;
- fluorouracil: 400 mg/m^2 intravenously on day 1 and 2400 mg/m^2 for 44–48 hours as continuous infusion. Cycles were repeated every 2 weeks for four cycles.

Dose modifications should be based on the preceding cycle nadir blood counts, biochemical profile and interim toxic effects. The doses of both cisplatin and fluorouracil should be decreased by 20% if any grade III or higher toxicities were observed. When a dose reduction is required, no dose escalation will be carried out subsequently. Chemotherapy will be delayed until the absolute neutrophil count recover to at least 1500/μL and the platelet count recover to at least 100 000/μL, and the chemotherapy will be stopped if there encounter any grade III or higher toxicity.

Salvage therapy

Salvage treatments containing reirradiation, chemotherapy and surgery will be given to patients after documented progression (relapse or distant metastasis), in accordance with the standard practice of guidelines.

Study participants

Inclusion criteria

Patients are eligible for this study if they fulfilled all of the following criteria:

- Previously untreated, biopsy-proven stage T3-4 and/or N+, resectable rectal adenocarcinoma with the tumours near anal verge within 12 cm
- Male or non-pregnant female
- Between 18 and 70 years of age
- Adequate haematologic function: white blood cell counts ≥4×10^9/L , neutrophils counts ≥1.5×10^9/L , platelet counts ≥1×10^9/L, haemoglobin ≥9 g/L
- Adequate renal function: creatinine ≤1.5× upper normal limit
- Adequate hepatic function: total bilirubin, Glutamic-oxalacetic transaminase (AST), Glutamic-pyruvic transaminase (ALT) level <2.0× upper normal limit)
- Satisfactory performance status: Karnofsky performance status (KPS) ≥70
- Approval from the ethics committee and prior written informed consents from all patients before registration were obtained

Exclusion criteria

- The evidence of relapse or distant metastasis
- Patients received treatment of other anticancer drugs or methods
- Patients have low compliance and are not able to complete the trial
- The presence of uncontrolled life-threatening diseases

Dropout or suspend of the trial

- Treatment delay for more than 2 weeks due to extended toxicity
- Severe treatment complications, such as
  - Grade III/IV allergic reaction
  - Grade IV neutropenia
  - Grade IV acute enteritis
- Disease progression during treatment
- Patient requests withdrawal from clinical trial
- Other potential situations that require the termination of research

Data analysis and sample size

This trial is performed to determine the maximum tolerance dose (MTD) of preoperative radiation dose by using GTV dose escalation scheme (6Gy×5, 7Gy×5, 8Gy×5). Primary endpoint to determine the MTD is any grade IV toxicity according to Common Terminology Criteria for Adverse Events (CTCAE)V.5.0. The sample size for this trial is calculated by the traditional 3+3 dose escalation scheme[27] as follows:

three patients receive the lowest level of radiation dose (5×6 Gy) to PTV-GTV in a cohort and dose-limiting toxicity (DLT) will be observed. If none of the patients show the DLT, another cohort of three patients will be enrolled to receive the next level of radiation dose (5×7 Gy). Three extra patients will be added to receive the same dose (5×6 Gy) if one patient exhibits the DLT. Of the total six patients treated at this dose level, the trial continues to the next dose level if only one out of six patients has experienced the DLT and stops at that dose level if at least two patients experience the DLT. When the escalation is stopped, additional three patients will be required to receive this dose level. The maximum sample size is 21 patients calculated as two dose levels with a maximum of six patients and nine patients at the MTD (figure 2).

OBSERVATION AND EVALUATION OF THE TRIAL

Pretreatment evaluation and screening

Each patient must complete the following items within 1 week before entering the trial:

- History review
- Physical examinations: including height and weight, digital rectal examination and regional lymph nodes examination
- Blood tests: including complete blood counts and biochemical profiles
- Tumour imaging: endoscopy ultrasound and MRI
- General check-up: ECG, chest X-ray
- History of current treatment and medications

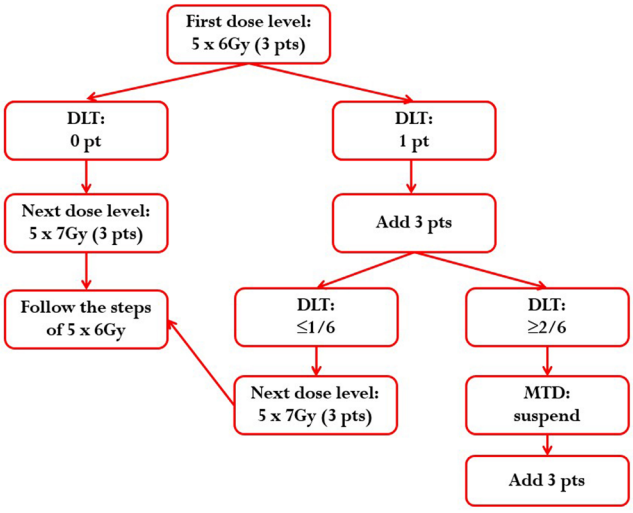

Figure 2 Graphical depiction of traditional 3+3 dose escalation methods for phase I cancer clinical trials. DLT, dose limiting toxicity; MTD, maximum tolerance dose; Pt, patient; Pts, patients.

- The qualification is confirmed and the informed consent is signed

During and post-treatment evaluation

Chemotherapy-related toxic effects and radiotherapy-related toxic effects will be assessed according to Common Terminology Criteria for Adverse Events (V.5.0).

- Laboratory examination: during the treatment period, complete blood counts and biochemical profiles will be checked once a week.
- Physical condition assessment: KPS score.
- Use of adjuvant drug: such as antiemetic drug, antidiarrhoeal and drugs for leucopenia and so on.
- Acute toxicity: including haematological toxicity, radiation-induced skin injury, radiation-induced enteritis and radiation-induced urinary system injury.

OUTCOMES MEASURE

Primary endpoint

- pCR rates: pCR is defined as a sterile specimen without residual cancer cells according to the Mandard classification system.[28] Standardised protocol to be used by qualified pathologist to evaluate the specimens within 4 weeks after surgery.[29]

Secondary endpoints

- R0 resection rate: R0 resection is defined as ≥1 mm non-involved circumferential resection margin, which is measured according to the pathological outcomes within 4 weeks after surgery.
- Sphincter preservation rate: measured according to the surgical outcomes within 4 weeks.
- Incidence of surgical complications: surgical complications are defined as those occurring within 30 days after surgery, such as reoperation, anastomotic fistula, bleeding, infection and death related to the operation.
- Incidence of acute toxicities during radiation or chemotherapy: number of participants with abnormal laboratory values and/or adverse events that are related to radiation or chemotherapy as assessed by CTCAE v5.0 within 3 months after surgery.

Follow-up after the trial

After completion of the study treatment, participants will be followed up every 3 months or as needed clinically in the first 2 years, every 6 months in the following 3 years, and annually thereafter. Follow-up examinations will include clinical assessment, contrast-enhanced MRI or CT, and blood testing including carcinoembryonic antigen (CEA). For tumour progression, treatment alternatives will be evaluated interdisciplinary considering choices of surgical resection, chemotherapy, reradiation therapy or other.

DISCUSSION

SCRT with sequential chemotherapy followed by surgery has been demonstrated as a potential alternative to conventional SCRT with immediate surgery for LARC. To further improve clinical outcomes, especially overall survival, we developed a novel preoperative SCRT regimen using GTV dose-escalation method (5×6 Gy, 5×7 Gy, 5×8 Gy) followed by mFOLFOX6 neoadjuvant chemotherapy in patients with LARC. Belluco *et al* studied the long-term outcome of patients treated with neoadjuvant chemoradiotherapy followed by surgery for T3 rectal cancer, and concluded that for patients who had complete pathological responses (pCR), 5 year overall survival were significantly better.[30] Khwaja SS *et al* reported that SCRT followed by mFOLFOX6 as preoperative regimen for rectal cancer resulted in stable patient-reported quality of life (QOL) outcomes 1 year after treatment.[21] These have motivated us to hypothesise that combining dosimetric and potentially biologic advantages of GTV dose escalation of SCRT and standard neoadjuvant chemotherapy could lead to improvement of pCR and long-term survival. Our study is aimed to lay the foundation for conducting future phase II/III clinical trials that may transform the preoperative treatment paradigm of SCRT from conventional 5×5 Gy to 5×6 Gy, 5×7 Gy or 5×8 Gy followed by mFOLFOX6 chemotherapy in patients with LARC.

Ethics/dissemination/confidentiality

We will fully inform the eligible patients of the purpose and procedures of this study. Written informed consent will be obtained after patients decide to participate. All clinical data are collected by research members confidentially. We will present our findings through scientific publication in international peer reviewed journals as well as at international and national conferences.

Biological specimens

Biological specimens (eg, biopsy tissue; blood for DNA extraction) will be obtained and stored in repositories

during the trial. Participants will be asked to sign a consent form to document their consent to the collection and submission of additional blood samples for storage and future testing (including genetic analysis).

Ancillary and post-trial care

Patients that are enrolled into the study are covered by indemnity for negligent harm through the standard National Health Service Indemnity arrangements. The University of Fujian Medical has insurance to cover for non-negligent harm associated with the protocol. This will include cover for additional healthcare, compensation or damages whether awarded voluntarily by the sponsor, or by claims pursued through the courts. Incidences judged to arise from negligence (including those due to major protocol violations) will not be covered by study insurance policies.

DATA COLLECTION/MANAGEMENT/ MONITORING

Data collection and management

Documents of the trial will be maintained for at least 5 years after the completion of the trial according to the Chinese Good Clinical Practice (GCP)-Regulation. The Research Unit of the Medical Affair Department of the XAHFMU will be responsible for archiving all relevant data of the trial.

Data safety monitoring board

The Institution Review Board of Fujian Medical University will act as the data safety monitoring board to monitor the recruitment, the report of adverse events, and the data quality semiannually.

Author affiliations
[1]Department of Radiation Oncology, Fujian Medical University Union Hospital, Fuzhou, Fujian, China
[2]Collogy of medical technology and engineering, Fujian Medical University Union Hospital, Fuzhou, Fujian, China
[3]Department of General Surgery, Fujian Medical University Union Hospital, Fuzhou, Fujian, China
[4]Department of Medical Oncology, Fujian Medical University Union Hospital, Fuzhou, Fujian, China
[5]Department of Radiation Oncology, Cancer Hospital of Fudan University, Shanghai, China
[6]Department of biomedical engineering, Innovative Cancer Institute, Miami, Florida, USA
[7]School of Clinical Medicine, Fujian Medical University, Fuzhou, Fujian, China

Contributors B-hX conceived and designed the study. MZ drafted the manuscript. MZ, X-yL and B-jG will in charge of conducting the trial. G-xG and PC contributed the section pertaining to surgery and will perform the surgery and assess postoperative situation of the patients. X-yL is responsible for chemotherapy aspect of study design and execution. B-hX and X-dX critically revised the manuscript for important scientific contents. All the authors provided approval of the final version for submission.

Funding Ben-hua Xu will have ultimate authority over the study design, conduct, data analysis and interpretation, manuscript writing and dissemination of results. Fujian Medical University Union Hospital.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol was approved by the Ethics Committee of Fujian Medical University Union Hospital (No. 2017YF020-02).

Provenance and peer review Not commissioned; externally peer reviewed.

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