Comparison of Outcomes and Side Effects for Neoadjuvant Chemotherapy with Weekly Cisplatin and Paclitaxel Followed by Chemoradiation versus Chemoradiation Alone in Stage IIB-IVA Cervical Cancer: study protocol for a randomized controlled trial

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Study protocol

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Abstract

Background

Currently, the standard treatment for locally advanced cervical cancer is concurrent chemoradiation (CCRT). The effect of neoadjuvant chemotherapy in advanced cervical cancer is controversial. Studies have shown that the addition of a weekly regimen of neoadjuvant chemotherapy (NACT) followed by CCRT may be superior to a triweekly regimen of NACT and CCRT. Among patients who had not received prior cisplatin, a cisplatin and paclitaxel (TP) regimen resulted in longer overall survival than other regimens. This study aims to investigate the feasibility, safety and efficacy of NACT with weekly TP followed by CCRT.

Methods

This is a prospective, randomized, open-labeled, multicentered Phase III study with a sample size of 300. Patients with IIB-IVA cervical cancer will be randomly allocated in a 1:1 ratio to one of two intervention arms. Study arm: patients will receive dose-dense cisplatin (40 mg/m^2) and paclitaxel (60 mg/m^2) weekly for 4 cycles followed by CCRT (45 Gy in 5 weeks concurrent with cisplatin 40 mg/m^2 weekly) plus image-guided adaptive brachytherapy (IGBRT). Control arm: patients will undergo CCRT treatment. The primary endpoints of the study are overall survival rate and disease-free response rate; the secondary endpoint is the response rate 3 months after treatment completion; the tertiary endpoints are grade 3–4 adverse effects and quality of life; and potential biomarkers for predicting treatment response will also be studied.

Conclusions

The data gathered from the study will be used to determine whether NACT with weekly TP followed by CCRT may become an optimized treatment for locally advanced cervical cancer.

Trial Registration

Chinese clinical trial registry, ChiCTR1900025327; http://www.chictr.org.cn. Registered 24 August 2019 - Retrospectively registered, medresman.org.cn/ChiCTR1900025326

Background

Cervical cancer, a considerable health crisis for women, is the fourth most common cancer worldwide and the fourth leading cause of cancer death [1]. The standard treatment for locally advanced cervical cancer (LACC) is currently concurrent chemoradiation (CCRT). However, the overall survival (OS) for stage IIB and

III-IV cancer is approximately 60–65% and 25%-50%, respectively, which are frustratingly low [2]. Therefore, it is imperative to develop new treatment strategies to improve survival.

Neoadjuvant chemotherapy (NACT) was first reported by Frei E [3]. The aim of chemotherapy preceding local modalities is to reduce the volume of the disease, making subsequent irradiation or surgery more effective while controlling micrometastatic disease. A comprehensive meta-analysis was performed including 4727 cases from 13 publications to precisely assess the prognostic role of NACT for LACC [4]. The response rate, specifically the clinical and pathological response to NACT, ranged from 58.49–86.54% and 7.5–78.81%, respectively; the treatment response indicated that LACC was sensitive to chemotherapy. In addition, the combined analysis showed that a better clinical response and pathologic response to NACT were associated with favorable PFS and OS. Para-aortic (PA) spread in cervical cancer is associated with a poor prognosis, despite the use of optimal first-line treatment, including chemoradiation therapy with extended field radiotherapy (EFR). Studies [5, 6] have suggested that adjuvant chemotherapy leads to better outcomes than chemoradiation therapy alone in PA-spread cervical cancer patients, despite increased toxicity.

NACT plays a yet unproved role in cervical cancer treatment, particularly when followed by CCRT, where data are scarce [7]. Traditional triweekly (once every 3 weeks) regimens of NACT followed by CCRT may not be superior to CCRT alone for the treatment of LACC [8, 9, 10]. Weekly regimens of NACT followed by CCRT may be superior to CCRT alone [8, 11, 12], and this approach is now being evaluated in a randomized trial in the UK (weekly paclitaxel and carboplatin for 6 weeks) (CRUK/11/024: INTERLACE trial) [13]. Among patients who had not received prior cisplatin, TP resulted in longer overall survival than TC[14]. Therefore, we will conduct this RCT to verify whether NACT with weekly cisplatin and paclitaxel followed by CCRT is superior to CCRT and as safe as CCRT.

Methods

Ethical approval

The study is being conducted in China. The study protocol was approved by Shanghai Jiaotong University School of Medicine affiliated with Ruijin Hospital Ethics Committee (N-2018-239). All the group members have GCP certificates. Any recorded results will be anonymized in our study database.

Study design

This is a prospective, randomized, open-labeled, multicentered phase III study. The 2-year progression-free survival in stage IIB-IVA cancer patients treated with CCRT is approximately 65% according to the literature. The desired 2-year progression-free survival treated with NACT followed by CCRT will be 80%. We assume an 8% loss to follow-up, and we seek a power of 80% at a two-sided significance level of 0.05. To detect a 15% difference, we will need 150 patients (per group). Based on an institutional volume of 80 patients per year and 20 patients per year in other centers, this trial will require 3 years to complete the recruitment of 300 patients. The objective is to explore the overall survival rate, disease-free response

rate, response rate 3 months after treatment completion, survival outcomes, quality of life and severity of side effects of dose-dense NACT followed by CCRT. The potential biomarkers for predicting treatment response will be studied.

Study organization

The study was designed by a team of researchers from Shanghai Jiaotong University Medical School affiliated with Ruijin Hospital. It is being conducted at 5 sites in China: Shanghai Jiaotong University Medical School affiliated with Ruijin Hospital, Renji Hospital, The First People's Hospital, Shanghai Tongji University affiliated with Oriental Hospital, and Fujian Medical University affiliated with Union Hospital.

Our group and its individual members have substantive experience in conducting studies on LACC. We have a multidisciplinary group to assess the stage and status of the patients precisely, to assure the patients meet the inclusion criteria, to treat the patients and monitor the side effects, and to follow the patients on a regular basis. Researchers will manage the whole process, and experienced statisticians will participate in the study design and data analysis.

Participants

We plan to recruit adult patients who have cervical cancer with the following inclusion and exclusion criteria.

Inclusion criteria

Each participant must meet all the following criteria to participate in this study: (1) age, 18~70 years; (2) histologically confirmed squamous carcinoma, adenocarcinoma or adeno-squamous carcinoma of the cervix; (3) FIGO (2009) stage IIB-IVA as evaluated by two senior gynecological oncologists; (4) performance status: Eastern Cooperative Oncology Group (ECOG) ≤2; (5) body weight ≥40 kg; (6) adequate bone marrow function (WBC $\geq 4.0\times10^9$/L, neutrophils $\geq 2.0 \times 10^9$/L, HB ≥70 g/L and platelets $\geq 100.0\times10^9$/L); adequate liver function (serum bilirubin, ALT, AST and ALP ≤1.0 N); adequate renal function (urea nitrogen ≤1.0 N, Cr≤1.0 N); (7) no active tuberculosis; (8) no pregnancy or lactation; (9) negative HIV test; and (10) written informed consent before enrollment and before initiation of any procedure.

Exclusion criteria

Individuals who meet any of the following criteria will be excluded from the study: (1) previous pelvic malignant diseases treated with chemotherapy or radiotherapy; (2) pelvic or abdominal radiotherapy; (3) suprarenal lymph node metastasis or distant metastasis detected by PET/CT or chest/abdominal CT; (4) acute infection or uncontrolled severe medical; (5) pregnant or lactating; (6) intestinal perforation or acute ileus; (7) uncontrolled cardiac disease (defined as a cardiac function that would preclude hydration during cisplatin administration and any contraindication to paclitaxel); (8) adrenocortical insufficiency; (9) bone marrow metastasis; or (10) not meeting requirements for chemotherapy.

Study procedures and treatments

The patients will be allocated in a 1:1 ratio to one of two intervention arms (Fig 1-2). The randomization scheme will be prepared by the study statistician using a random number table, with the results entered by a study manager not involved with patient recruitment. During treatment, patients will have gynecological oncologist visits before each day of chemotherapy during NACT and weekly visits during CCRT.

Clinical data The data collected will include general medical information (age, childbirth, family history of cancer, and chronic diseases), tumor stage, tumor type, and chemo-/radiotherapy-related adverse events. At baseline, all patients will be physically examined by two gynecological oncologists and will have computed tomography (CT-scans) of the chest and upper abdomen or 18-fluoro-2-deoxy-D-glucose positron emission tomography ([18F] FDG-PET) with computed tomography (CT) (PET/CT) and magnetic resonance imaging (MRI)/computed tomography of the pelvis (within the previous 4 weeks). Full blood counts, liver and renal function tests will also be performed, and human papillomavirus (HPV) type and tumor marker (SCCA, CA 125, CA 199) values will be determined. In all cases, a detailed drawing of the lesion will be registered, and glomerular filtration rate (GFR), computed tomography urography (CTU), cystoscopy and sigmoidoscopy will be performed when necessary. All histology slides will be reviewed by the same panel of pathologists.

Control arm Patients will undergo radiation with concomitant cisplatin (CCRT) treatment as follows: cisplatin (40 mg/m^2) will be given with hydration over 1 h (before radiation), weekly for 5 cycles. Radiotherapy to the whole pelvis will be given to a total dose of 45 Gy in 5 weeks. Extended fields will be used to treat positive common iliac and/or para-aortic lymph nodes with a total dose of 55-60 Gy. Brachytherapy will be given following completion of external beam radiation therapy. Patients will receive image-guided adaptive brachytherapy (IGBRT) with a high-risk clinical target volume (HRCTV) of 85 Gy in 3-4 fractions.

Study arm Neoadjuvant chemotherapy will be given weekly for 4 weeks (on days 1, 8, 15 and 22) as follows: paclitaxel (60 mg/m^2) over 1 h followed by cisplatin (40 mg/m^2) over 30 min, given intravenously with hydration for 3 days (3000 ml per day, from the day before the dose to the day after the dose). Both drugs will be delayed if neutrophils are $<1.5\times10^9$/L and/or platelets are $<75\times10^9$/L on the day of treatment until hematologic improvement to grade 1 is achieved. The doses of paclitaxel and cisplatin will be reduced by 50% if neutrophils are $(0.5\text{-}1.0)\times10^9$/L and/or platelets are $(25\text{-}50)\times10^9$/L. In the event of further hematological toxicity (neutrophils $<0.5\times10^9$/L and/or platelets $<25\times10^9$/L), NACT will be discontinued. Patients with a significant hypersensitivity reaction to paclitaxel or cisplatin will be withdrawn from the study. If NACT is discontinued early, patients who proceed to CCRT will commence when blood counts have recovered. Within 2 weeks after NACT, patients will be treated subsequently by CCRT as the control arm as soon as hematological recovery permits.

Follow-up After completion of treatment, patients will be followed up every 3 months during the first 2 years and every 6 months for the next 3 years. Gynecological oncologist examination will be repeated after NACT, 12 weeks after CCRT and again 3-6 months after treatment. Abdominal ultrasound or upper abdomen CT, pelvic MRI, and tumor marker values will be evaluated. PET/CT, GFR, and CTU will be performed when necessary.

Study outcomes

Primary endpoint The primary aim of this trial will be to compare the 2-year disease-free survival (DFS) difference between dose-dense NACT followed by CCRT and CCRT alone. Five-year overall survival (OS) and disease-free survival (DFS) rates will be recorded. We will test the hypothesis: compared with CCRT alone, dose-dense NACT followed by CCRT can significantly improve 2-year DFS and 5-year OS and DFS in stage IIB-IVA cervical cancer patients.

Secondary endpoint The secondary specific aim of this trial will be a comparison of the response rate 3 months after treatment completion. In addition, the response rate for NACT will also be recorded. The response rate will be assessed by two radiologists blinded to the treatment option based on RECIST 1.1 criteria. We will test the hypothesis: dose-dense NACT followed by CCRT will have a higher response rate at 3 months than CCRT alone.

Tertiary endpoint The tertiary specific aim of this trial will be to measure the difference in adverse effects and quality of life between the two groups. All grade III/IV acute and late toxicities will be considered significant. We will measure quality of life with the EORTC QLQ-30 (V3.0) and CX24. We will test the hypothesis: there will be no difference in the incidence and severity of therapy-attributed adverse events between the two groups. Dose-dense NACT followed by CCRT will result in a higher quality of life than CCRT alone.

Quaternary endpoint The quaternary specific aim of this trial will be to identify predictive biomarkers of treatment response. By collecting tissue and blood samples, including samples from recurrent tumors, before and after NACT and before and after CCRT (if there is residual tumor available after treatment), we intend to compare differences in gene expression profiles in responding and nonresponding subgroups in each treatment arm. We will test the hypothesis: there will be different gene expression profiles in responding and nonresponding groups, independent of the treatment group assignment.

Clinicalresponse Clinical remission will be evaluated according to the World Health Organization (WHO) criteria, the Response Evaluation Criteria in Solid Tumors (RECIST) [15]. A pelvic MRI will be performed at the end of the 4 weeks of NACT to assess the response using the RECIST 1.1 criteria. The overall response will be determined using pelvic MRI 12 weeks after the completion of CCRT. MRI scans will all be reviewed at Ruijin Hospital and assessed by two radiologists blinded to the treatment option based on the RECIST 1.1 criteria. Further radiological assessments will be conducted as clinically indicated. The complete response (CR) is defined as disappearance of all target lesions, and any pathological lymph nodes (whether target or nontarget) must have reduction in the short axis to < 10 mm. Partial remission

(PR) is defined as at least a 30% decrease in the sum of the diameters of the target lesions, taking as reference the baseline sum of the diameters. Progressive disease (PD) is defined as at least 20% increase in the sum of the diameters of the target lesions, taking as reference the baseline sum of the diameters, with the smallest sum of increase at least 5 mm. In addition, a relative increase of more or new lesions is also considered progression. Stable disease (SD) is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Patients with CR or PR will be classified as clinical responders, and patients with stable disease and progression of disease will be defined as clinical nonresponders. If the two radiologists reached different conclusions, the results will be rechecked and discussed to reach a consensus.

Adverse effects The adverse effects of adjuvant chemotherapy and chemoradiation will be evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All patients will be monitored for marrow function suppression as well as gastrointestinal and dermatologic side effects. Full blood counts will be performed weekly during NACT and twice weekly during CCRT. Biochemistry and toxicity assessments will be carried out weekly during treatment, then 3 months post-CCRT, and every 12 months for 5 years. A bone density test will be performed before treatment and 3 months after CCRT. Adverse events will be based on the maximum toxicity grade for each type of event. All grade 3/4 acute and late toxicities will be considered significant. Serious adverse events need to be addressed urgently and should be reported to the functionary within 24 h. Adverse events occurring 6 months after the end of treatment will be considered late toxicity. Quality of life will be assessed with the EORTC QLQ-30 (V3.0) and CX24 before treatment, post-NACT, post-CCRT, three months post-CCRT, and every 12 months for 5 years.

Statistical analysis

Baseline characteristics (age, tumor size, tumor stage, etc.) for both treatment groups will be compared to ensure comparability of the patient populations to rule out selection bias. Means and standard deviations will be used to report continuous variables, and proportions will be used to report categorical variables. Comparisons of categorical outcome measures such as response rate, survival rate, incidence of adverse effects, etc. will be computed using the chi-square test or Fisher’s exact test if any of the expected values in the contingency table are less than 5. Kaplan-Meier survival analysis will be used for 2-year and 5-year overall survival and disease-free survival comparisons. Relative risks, or odds ratios, with their corresponding 95% confidence intervals will be analyzed by multivariable logistic regression. A P-value of <0.05 was considered significant.

Discussion

Despite the availability of an effective screening program and the papillomavirus vaccine, a large proportion of patients are not discovered to have cervical cancer until they have reached an advanced stage and suffer from local recurrences and distant metastases. The Cochrane meta-analysis reported a stage-dependent advantage of CCRT over radiotherapy (RT), with 5-year survival benefits of 10% for

women with stages IB to IIA cervical cancer, 7% for women with stage IIB cervical cancer, and 3% for women with stage III to IVA cancer [16]. Improving the survival of these patients is an urgent issue.

Some researchers have studied the effect of NACT prior to CCRT. Studies have shown traditional triweekly platinum-based NACT followed by CCRT has been applied to LACC patients. Narayan et al [9] retrospectively compared the effect of 2 cycles of triweekly TPF (cisplatin+paclitaxel+5-flurical) or TF (cisplatin+5-flurical) followed by CCRT vs. CCRT alone in 723 stage IIB-IIIB cervical cancer patients. They found that NACT followed by CCRT could improve 5-year progression-free survival (58.3% vs 41.8%) but had no impact on overall survival. Marita [17] retrospectively analyzed the survival of 207 stage IIB-IIIB cervical cancer patients who received 2-4 cycles of platinum-based NACT prior to CCRT. The results revealed that the 5-year survival rates for stage IIB-IIIA and IIIB were 84% and 61%, respectively, which are superior to the survival rates of traditional CCRT reported in the literature. A randomized open-label phase II trial enrolled 107 patients, 55 randomly assigned to the NACT arm and 52 to the CCRT-alone arm. NACT was associated with an inferior 3-year PFS (40.9% vs. 60.4%), a lower 3-year OS rate (60.7% vs. 86.8%), and a lower complete response rate (56.3% vs. 80.3%) [10].

In addition, a meta-analysis of 21 randomized trials showed no increase in OS despite a significant reduction in tumor volume by primary chemotherapy in a comparison of radiotherapy alone with radiotherapy preceded by chemotherapy. However, subgroup analysis showed a 7% improvement in the 5-year OS with a chemotherapy cycle length of <14 days over that shown in studies with longer cycle lengths, and cisplatin dose intensities $\geq$ 25 mg/m^2 per week tended to show a survival advantage [8]. Regarding the distribution and metabolism of these drugs, Mori [18] found that paclitaxel was retained in cervical cancer tissues for 6 days after intravenous administration of a 60 mg/m^2 dose, but it could not be detected after 2 weeks, suggesting that a weekly schedule was most effective for tumor cell death rather than the standard triweekly regimen. Thus, administering NACT at shorter intervals (dose-dense) may result in enhanced cell death and overcome accelerated repopulation. A dose-dense (weekly) schedule is likely to result in improvement in outcome.

The initial results from two phase II studies [11-12] have been reported on patients who received NACT using weekly paclitaxel (60-80 mg/m^2) and carboplatin (AUC=2) for 6 weeks followed by CCRT. Following NACT, a response rate of 67.5-70% was achieved, mostly partial responses. Post-CCRT, 85-100% of eligible patients achieved CR. Grade 3-4 hematologic toxicity was observed in approximately 20% of patients. A 3-year overall survival rate of 68% was observed in 42 stage IB2-IVA patients. These observations are encouraging. The approach is now being evaluated in a randomized trial in the UK (CRUK/11/024: INTERLACE trial) [13].

The combination of paclitaxel and carboplatin has been used in a weekly schedule; this combination maximizes the potential additive/synergistic interactions with different mechanisms of action. However, a phase II nonrandomized trial reported that two cycles of weekly cisplatin (35 mg/m^2) combined with gemcitabine (1000 mg/m^2) as an upfront treatment for IB2-IVA patients managed with CCRT did not result in a meaningful improvement in ORR [19].

Which NACT regimen is the best? Regarding chemotherapy in the treatment of advanced metastatic or recurrent cervical cancer, cisplatin has been considered the most effective agent. The cisplatin/paclitaxel (TP) combination is superior to other regimens. In a phase III trial comparing four regimens (cisplatin/paclitaxel, cisplatin/vinorelbine, cisplatin/gemcitabine, cisplatin/topotecan), cisplatin/paclitaxel appears superior to the others [20]. According to the results from JCOG0505, among patients who had not received prior cisplatin, TP resulted in longer overall survival than TC (23.2 months vs. 13.0 months) [14].

Based on these data, we consider weekly paclitaxel (60 mg/m^2) and cisplatin (40 mg/m^2) for 4 weeks as the first-line choice for the NACT regimen, and we aim to conduct a randomized trial to compare the survival outcomes of this NACT regimen followed by CCRT with those of CCRT alone for newly diagnosed stage IIB-IVA cervical cancer patients. The response rates, adverse effects, and quality of life will also be assessed, and potential biomarkers for predicting treatment response will be studied. If a superior therapeutic effect is confirmed, NACT with weekly TP followed by the CCRT procedure may become an optimized method of cancer treatment.

Trial Status

Protocol version number and date

Chinese clinical trial registry, ChiCTR1900025327; http://www.chictr.org.cn. Registered 24 August 2019. Retrospectively registered, medresman.org.cn/ChiCTR1900025326

The date recruitment began 01-01-2019

The approximate date when recruitment will be completed 12-31-2026

Abbreviations

CCRT: Concurrent chemoradiation; NACT: Neoadjuvant chemotherapy; IGBRT: image-guided adaptive brachytherapy; LACC: Locally advanced cervical cancer; OS: Overall survival; PA: Para-aortic; EFR: Extended field radiotherapy; AUC: Area under the curve; ECOG: Eastern Cooperative Oncology Group; WBC: White blood cell; HB: Hemoglobin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; Cr: Creatinine; HIV: Human immunodeficiency virus; CT: Computed tomography; FDG-PET: 18-Fluoro-2-deoxy-D-glucose positron emission tomography; PET-CT: 18-Fluoro-2-deoxy-D-glucose positron emission tomography with computed tomography; MRI: Magnetic resonance imaging; HPV: Human papillomavirus; SCCA: Squamous cell carcinoma antigen; CA 125: Carbohydrate antigen 125; GFR: Glomerular filtration rate; CTU: Computed tomography urography; HRCTV: High-risk clinical target volume; DFS: Disease-free survival; WHO: the World Health Organization; RECIST: the Response Evaluation Criteria in Solid Tumors; CR: Complete response; PR: Partial remission; PD: Progression disease; SD: Stable disease; CTCAE: the Common Terminology Criteria for Adverse Events; RT:

Radiotherapy; TPF: Cisplatin/paclitaxel/5-flurical; TF: Cisplatin/5-flurical; TP: Cisplatin/paclitaxel; TC: Carboplatin/paclitaxel

Declarations

Ethics approval and consent to participate

The study was approved by Shanghai Jiaotong University School of Medicine Ruijin Hospital Ethics Committee. (2018-239)

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

Self-raised fund supports this study.

Authors' contributions

WF, JL and RC developed the protocol and grant proposal for this project and wrote the manuscript. YL, HL, LS and WL contributed to the protocol and grant proposal. CY, HX and WX assisted with writing and editing of the manuscript. The manuscript was amended based on comments from all authors. All authors read and approved the final manuscript.

Data availability statements

Not applicable.

Acknowledgment

The authors thank all of the study participants for their great effort. Furthermore, the founding body was not involved in the study design and will not be involved in the collection, analysis, and interpretation of data, in the writing of the manuscript and in the decision to submit the manuscript for publication.

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Figures

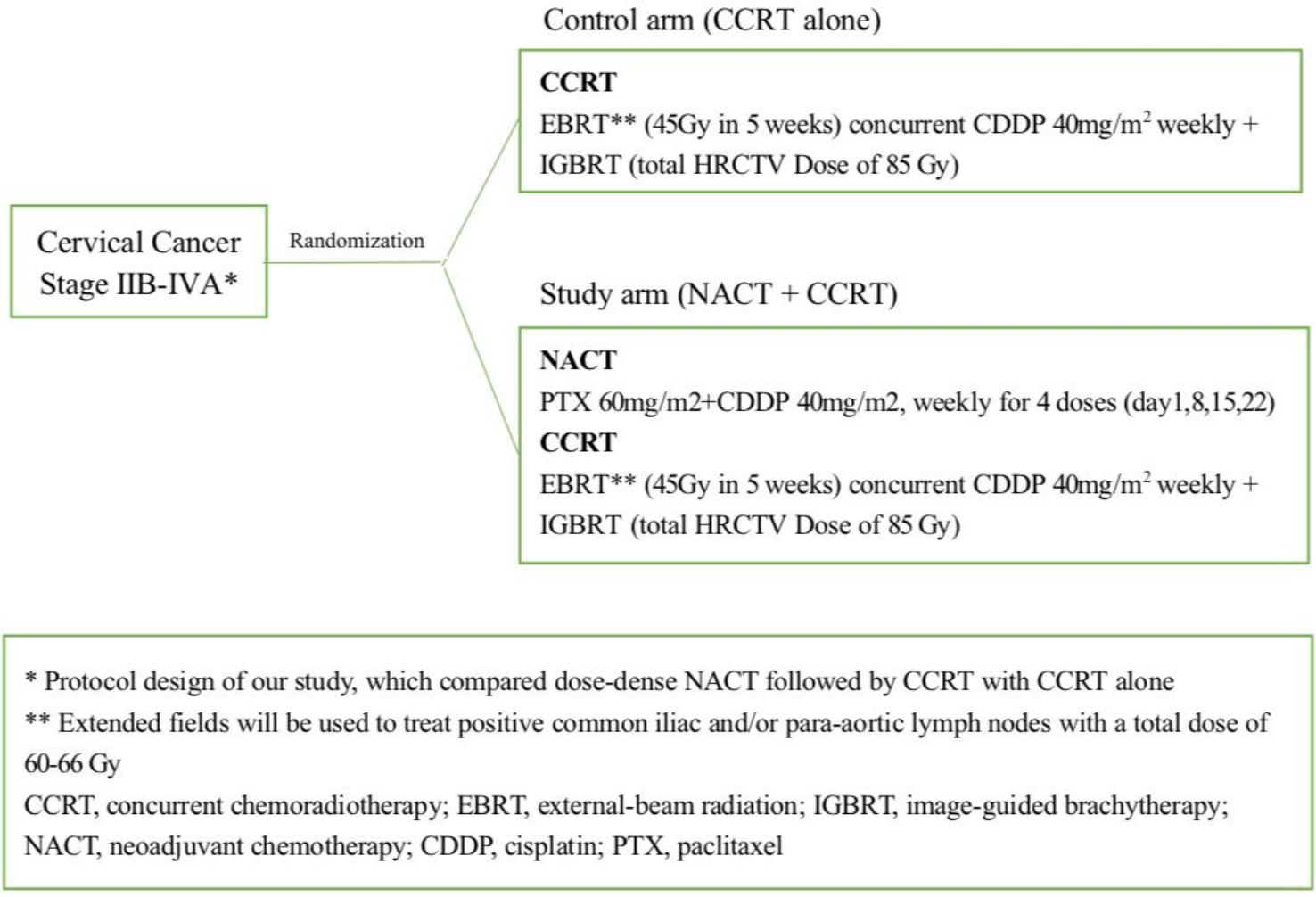
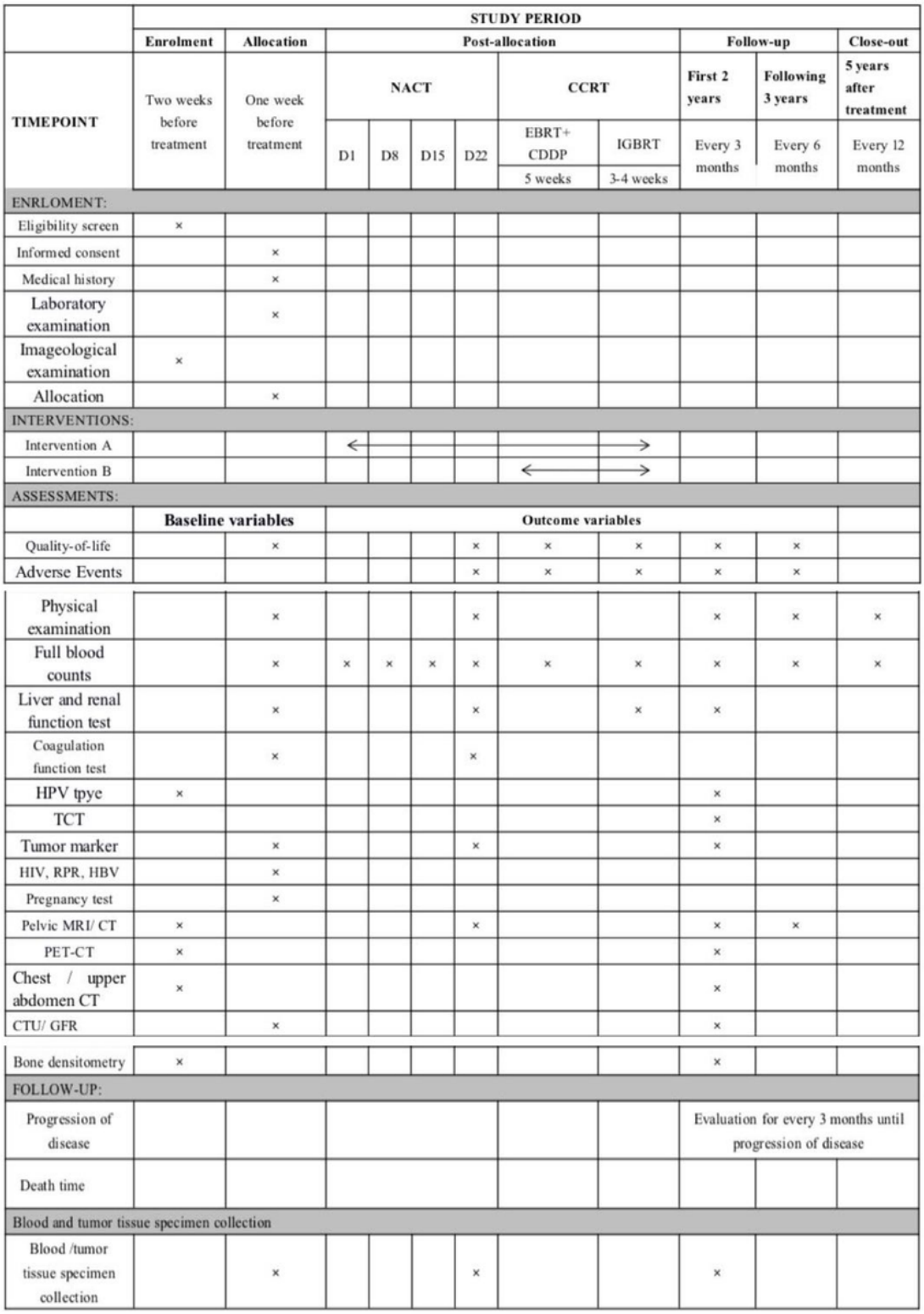


Figure 1

Protocol design (Study procedures and treatments, paragraph 1)



	STUDY PERIOD										
	Enrolment	Allocation	Post-allocation						Follow-up		Close-out
TIMEPOINT	Two weeks before treatment	One week before treatment	NACT				CCRT		First 2 years	Following 3 years	5 years after treatment
			D1	D8	D15	D22	EBRT+ CDDP 5 weeks	IGBRT 3-4 weeks	Every 3 months	Every 6 months	Every 12 months
ENRLOMENT:											
Eligibility screen	×										
Informed consent		×									
Medical history		×									
Laboratory examination		×									
Imageological examination	×										
Allocation		×									
INTERVENTIONS:											
Intervention A			←	—	—	—	—	→			
Intervention B							←	→			
ASSESSMENTS:											
	Baseline variables		Outcome variables								
Quality-of-life		×				×	×	×	×	×	
Adverse Events						×	×	×	×	×	
Physical examination		×				×			×	×	×
Full blood counts		×	×	×	×	×	×	×	×	×	×
Liver and renal function test		×				×		×	×		
Coagulation function test		×				×					
HPV tpye	×								×		
TCT									×		
Tumor marker		×				×			×		
HIV, RPR, HBV		×									
Pregnancy test		×									
Pelvic MRI/ CT	×					×			×	×	
PET-CT	×								×		
Chest / upper abdomen CT	×								×		
CTU/ GFR		×							×		
Bone densitometry	×								×		
FOLLOW-UP:											
Progression of disease									Evaluation for every 3 months until progression of disease		
Death time											
Blood and tumor tissue specimen collection											
Blood /tumor tissue specimen collection		×				×			×		

Figure 2

Study period

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITChecklist.docx