


BMJ Open Multicentre, randomised controlled trial of adjuvant chemotherapy in cervical cancer with residual human papilloma virus DNA following primary radiotherapy or chemoradiotherapy: a study protocol

Yanhong Wang ,¹ Yi Ouyang,² Jingjing Su,¹ Jing Liu,³ Qunrong Cai,¹ Qin Xu,³ Zhigang Bai,¹ Xinping Cao²

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YW and YO contributed equally. ZB and XC contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Dr Xinping Cao;
caoxp@systucc.org.cn

ABSTRACT

Introduction The role of adjuvant chemotherapy after radical radiotherapy (RT) or chemoradiotherapy (CRT) in cervical cancer awaits further confirmation. Evidences have shown that persistent human papilloma virus (HPV) DNA in exfoliated cell post-RT is a potential biomarker of subclinical residual disease and thus increases the risk of recurrence. In this prospective, multicentre, randomised controlled trial, we will use HPV DNA in exfoliated cell to identify patients with cervical cancer who received definitive RT or CRT with higher risk of relapse for adjuvant chemotherapy.

Methods and analysis Eligible patients with histologically confirmed cervical cancer stage IIA2 to IVA of the International Federation of Gynaecology and Obstetrics, adequate organ function and no locoregional disease or distant metastasis after completion of primary treatment will be screened for HPV DNA in exfoliated cell at 1 month post-RT. Patients with undetectable HPV DNA will undergo standard surveillance. Patients with detectable HPV DNA will be randomly assigned to either adjuvant chemotherapy with docetaxel and nedaplatin for four cycles (arm 1) or observation (arm 2). Patients will be stratified for primary treatment (RT vs CRT). The primary endpoint is relapse-free survival.

Ethics and dissemination This protocol received a favourable ethical opinion from the Ethics Committee of the Second Affiliated Hospital of Fujian Medical University on 6 February, 2018, (No. 28). The trial results will be published in peer-reviewed journals and presented in conferences. A summary of the findings will be made available to participants.

Trial registration number ChiCTR-IIR-17012655; Pre-results.

INTRODUCTION

Cervical cancer remains to be one of the most common tumours affecting women worldwide, ranking third for cancer incidence and fourth for mortality.¹ In China, approximately

Strengths and limitations of this study

- This is the first study to investigate the efficacy of adjuvant chemotherapy for patients with cervical cancer who have residual human papilloma virus (HPV) DNA at 1 month post-radical radiotherapy (RT) or chemoradiotherapy (CRT).
- Previous studies have reported that patients with cervical cancer with persistent HPV after radical RT or CRT would have a higher recurrence rate and worse survival than patients with cleared HPV DNA; thus, we propose to include post-RT HPV DNA as a non-anatomical determinant of risk classification and treatment selection for adjuvant therapy in cervical cancer.
- A study showed that prognostic accuracy of HPV test was highest at 3 months (82%), but, considering prognostic accuracy and impact of overall treatment time on survival, this study focuses on patients with persistent HPV DNA at 1 month, which may lead to false-positive results.
- If relapse-free survival is greater in patients treated with adjuvant chemotherapy, this study will provide a new standard of care for patients with cervical cancer with residual HPV DNA, and HPV DNA persistence will be identified as one of the indications of adjuvant chemotherapy for patients with cervical cancer treated with curative RT or CRT.

98 900 women developed this disease, and 30 500 women died in 2015.²

Adjuvant chemotherapy following radiotherapy or chemoradiotherapy

For locally advanced cervical cancer, curative-intent chemoradiotherapy (CRT) is the mainstay of treatment, and most patients will achieve complete clinical remission. However, the disease will subsequently recur

in 30% to 40% of patients either at the locoregional site or through distant metastasis, which prevents long-term cure.^{3,4} Thus, adjuvant chemotherapy has been studied to improve the efficacy. In 2011, Dueñas-González *et al* published a Consolidated Standards of Reporting Trials study in which 259 patients were submitted to concurrent CRT (cisplatin 40 mg/m² and gemcitabine 125 mg/m² weekly for 6 weeks), followed by two cycles of adjuvant chemotherapy (cisplatin 50 mg/m² on day 1, plus gemcitabine 1000 mg/m² on days 1 and 8) and 255 patients were assigned to concurrent cisplatin (40 mg/m²) treatment and radiotherapy (RT). This study showed that adjuvant chemotherapy after concurrent CRT conferred superior progression-free survival over CRT (74.4% vs 65% at 3 years).⁵ Dr. Wang also reported that, for locally advanced cervical cancer, concurrent cisplatin (40 mg/m² weekly) treatment and RT plus adjuvant chemotherapy (docetaxel 60 mg/m² was used on day 1, cisplatin 40 mg on days 1 to 3, three cycles) could improve short-term and long-term survival and local control rate with tolerated toxicities compared with RT alone.⁶ Although the addition of adjuvant chemotherapy plus concurrent CRT rendered better survival than CRT or RT alone, the relative contribution of concurrent and adjuvant components of chemotherapy has not been adequately evaluated, and the extent to which adjuvant chemotherapy can affect survival in cervical cancer awaits further study. Adjuvant chemotherapy after RT alone or CRT did not improve disease-free survival and overall survival (OS) in another randomised controlled trial. In this trial, mitomycin C and oral 5-fluorouracil (5-FU) was administered concurrently with RT, and maintenance oral 5-FU was administered as adjuvant chemotherapy.⁷ Not all patients will likely gain from adjuvant chemotherapy after CRT or RT alone, so the key point is in patient selection to maximise the magnitude of benefit.

Relationship of human papillomavirus with prognosis of cervical cancer after RT

The involvement of human papilloma virus (HPV) in the development of cervical cancer has been firmly established, and >90% of patients harbour HPV in their tumour cells.^{8,9} Furthermore, for patients with cervical cancer treated with radical RT or CRT, pretreatment HPV infection is associated with better survival and lesser recurrence compared with HPV-negative tumour, which may be interpreted by the fact that irradiation interferes the E6/E7 inactivation p53/pRb and renders HPV-positive cancer cells more responsive to therapy.^{10–13}

It also has been reported that residual HPV DNA is clinically useful as a new marker to predict local recurrence after conization for cervical intraepithelial neoplasia^{14–18} and after RT for invasive cervical carcinoma.^{19–28} In the study conducted by the University of the Ryukyus in Japan, local recurrence rate was significantly higher in patients with persistent HPV than in patients cleared for HPV who were treated with RT (34% vs 7.1%). Multivariate analysis showed that persistence of HPV infection exhibited the

largest HR values and smallest p values, which suggested that HPV persistence was the most powerful independent predictor for local disease-free survival and OS.²¹ Datta *et al* have reconfirmed that patients with reduction $\geq 99.5\%$ in HPV titers at baseline had better survival outcome than those with reduction $< 99.5\%$.²⁰

Another study analysed the correlation of HPV prevalence in the exfoliated cell with recurrence in post-RT cervical carcinoma. It indicated that HPV persistence in exfoliated cell had high sensitivity (100%) in detecting recurrence after RT and further suggested that the presence of latent tumour cells with residual HPV infection, which were resistant to therapy, maybe the origin of recurrence.²² This conclusion was further strengthened by Italian researchers: 16 patients with locally advanced cervical cancer were treated with CRT followed by radical surgery, and majority of the women cleared of HPV had pathologically complete response (pCR), 6/6), while only 40% of patients with persistent HPV achieved pCR. It suggested that residual HPV DNA may exist in silent tumour cells, which maybe the source of high local relapse rate.¹⁹ Moreover, they demonstrated that the HPV type, physical status and point mutation after RT were exactly similar to those at the onset of therapy, which indicated that viral persistence rather than re-infection occurs in these patients.

As stated above, a detectable HPV DNA after RT represents a biomarker of subclinical residual disease and is a valid tool for assessing the risk of recurrence. Because of the generally poor salvage rate of the central recurrences of locally advanced cervical cancer and grave symptoms of patients with uncontrolled recurrent pelvic disease, the value of adjuvant therapy to eradicate the subclinical disease could be tremendous.

Timing of HPV test after RT or CRT

HPV DNA may be persistently detected after RT in tumours because HPV DNA fragments may be present in degraded tumour cells even after all cancer cells have been eradicated.²⁹ Song *et al* performed the HPV test on every patient visit and evaluated the association of HPV results with prognosis. They suggested that prognostic accuracy of HPV test was highest at 3 months (82%).³⁰ To our knowledge, worse treatment outcomes can be expected with prolonged overall treatment time (OTT) during definitive or adjuvant CRT for cervical cancer.^{31–34} If adjuvant chemotherapy was administered to patients with persistent HPV at 3 months, it would be too late to effectively eradicate subclinical residual tumour cells and reduce the recurrence rate. Considering the adverse effect of OTT, an HPV test at 1 month is adopted in our study, as it has secondary sensitivity and specificity only to that of 3 months.

We presume that patients with cervical cancer with detectable post-RT HPV have a significant likelihood of developing local recurrence, and administration of adjuvant chemotherapy can significantly improve local control and, therefore, relapse-free survival (RFS) by eradicating

silent tumour cells. Correlation of post-RT HPV DNA and clinical outcome is a secondary endpoint of the study.

METHODS AND ANALYSIS

Study design and treatment

This is a multicentre, randomised controlled trial which will investigate whether adjuvant chemotherapy can reduce recurrence rate and improve RFS compared with observation in patients with cervical cancer with persistent HPV after RT. RT alone or concurrent CRT will be stratified in both treatment arms. This study is funded by Science and Technology Planning Project of Quanzhou Science and Technology Bureau and Fujian Provincial Health and Family Planning Commission Research Talent Training Project.

Sample-size calculation

As the role of adjuvant chemotherapy after radical RT is uncertain, a meta-analysis of 3-year RFS for adjuvant chemotherapy after RT was conducted. Data of RFS was extracted from three prospective studies, and the HR of the 3-year RFS is 0.74 (95% CI 0.63 to 0.84).^{5 7 35} We presume that patients with cervical cancer with persistent HPV at 1 month post-RT will gain more advantage from adjuvant chemotherapy than all patients with cervical cancer. Therefore, with an estimated HR of 0.74 (observation arm as reference), approximately 295 patients will be required with a power of 0.8, α of 0.05 and a dropout rate of 10%.

Study setting

The study will be conducted at the Second Affiliated Hospital of Fujian Medical University, Sun Yat-sen University Cancer Center (SYSUCC) and Fujian Provincial Tumor Hospital. The study will run for 7 years between 1 March, 2018, and 28 February, 2025. All sites have existing personnel experienced in the treatment of cervical cancer and HPV test.

Study endpoints

The primary endpoint is RFS, with secondary endpoints including OS, local relapse-free survival, distant failure-free survival, incidence of adverse events and correlation of HPV DNA and clinical outcome.

Eligibility criteria

Patients with locally advanced cervical cancer diagnosed as stage IIA2 to IVA according to the International Federation of Gynaecology and Obstetrics (FIGO) who meet the inclusion criteria and dissatisfy the exclusion criteria described below will be considered eligible.

Inclusion criteria

1. Newly diagnosed and histologically confirmed cervical cancer.
2. Age ≥ 18 and ≤ 70 years at the time of consent.
3. Positive HPV DNA at diagnosis.
4. FIGO stage IIA2 to IVA.

5. No clinical evidence of distant metastasis at diagnosis.
6. Achievement of clinical complete remission at 1 month after completion of primary RT or CRT.
7. Persistence of the same type HPV DNA in the exfoliated cell at 1 month post-RT.
8. Good general health condition (Eastern Cooperative Oncology Group score 0 or 1).
9. Laboratory findings within the following ranges (at ≤ 14 days prior to enrolment): leucocyte count $\geq 3.0 \times 10^9/L$, neutrophil count $\geq 1.5 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$, total bilirubin level $\leq 1.5 \times$ upper limit of normal (ULN), aspartate aminotransferase/alanine aminotransferase level $< 2.5 \times$ ULN and creatinine clearance > 50 mL/min.
10. Signed informed consent and appropriate compliance to ensure follow-up visit.

Exclusion criteria

1. Pregnancy or lactation.
2. Previous (< 5 years) malignancy (except cured skin cancer).
3. > 12 weeks after completion of primary RT.
4. Receipt of prior neoadjuvant chemotherapy.
5. Serious complication that affects tolerance to treatment.

Informed consent

Eligibility to participate will be confirmed by a clinician prior to obtaining consent. Patients will be given at least 24 hours to consider the patient information sheet and time to ask questions prior to obtaining written informed consent by a trial doctor. Before each HPV test, informed consent will have to be signed (online supplementary appendix 1).

Randomisation

Randomisation will be administered centrally by the SYSUCC. Eligible patients will be randomly allocated using the random number table. Randomisation will be conducted 1:1, with stratification for the type of primary treatment (RT or CRT), to either adjuvant chemotherapy (arm 1) or surveillance only (arm 2).

Blinding

There will be no blinding in this study.

Workflow

HPV DNA will be tested prior to the start of RT and also at 1 and 3 months post-RT. Cervical cells for the HPV DNA test will be collected using the cervical cell capture kit (HybriBio Limited Corp, Chaozhou, China). This consists of a cervical brush and one tube with 3 mL of specimen transport medium. The brush will be rotated clockwise three to five times in full turns in the endocervical os and swabbed on the ectocervical epithelium and then placed in the specimen transport media. The specimens will be stored at 4°C before HPV DNA testing. The presence of HPV will be examined by using flow-through hybridisation and gene-chip technology, which can detect 15

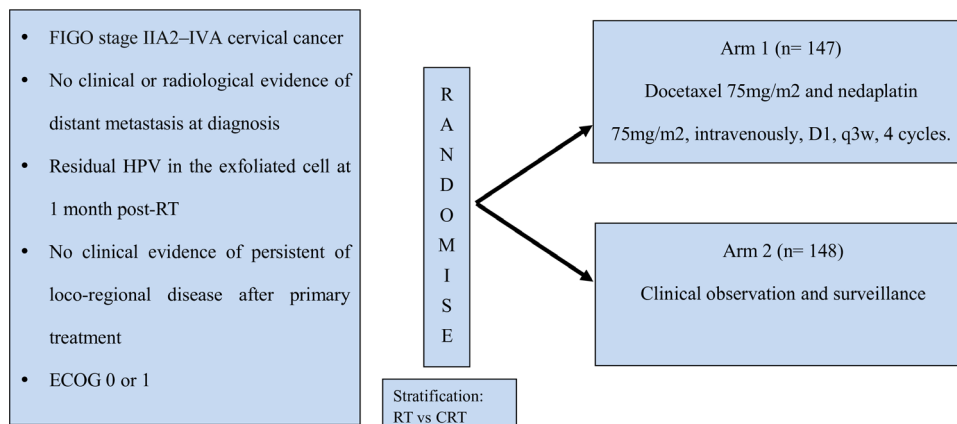


Figure 1 Trial flowchart. CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; HPV, human papilloma virus; RT, radiotherapy.

high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66 and 68) and 6 low-risk HPV types (6, 11, 42, 43, 44 and C-CP8304).

All pretreatment screening procedures have to be completed within 4 weeks before randomisation, which consist of demographic data, medical history, disease history (including date of initial diagnosis, histology and status of regional lymph nodes, FIGO stage), complete physical examination (including performance status (PS), body weight, height and vital sign of vagino-recto-abdominal examination), baseline laboratory tests (haematology, biochemistry and hepatitis B surface antigen), electrocardiography, tumour biomarker (squamous cell carcinoma antigen, cancer antigen-125 and carcinoembryonic antigen), colour Doppler of supraclavicular and inguinal lymph nodes, chest CT, MRI of the abdomen and pelvis and bone scan. In arm 1, patients will receive docetaxel 75 mg/m² and nedaplatin 75 mg/m² intravenously, both administered on day 1 every 3 weeks for a total of four cycles. Cisplatin or carboplatin administered on day 1 will be used to replace nedaplatin when significant (grade ≥ 3) thrombocytopenia or allergy exists (figure 1).

During adjuvant chemotherapy, laboratory haematology, biochemistry and adverse events will be assessed weekly of each cycle. Adverse events will be graded according to Common Terminology Criteria for Adverse Events (V.3). When the absolute neutrophil count is $< 1.5 \times 10^9/L$ or platelet count is $< 75 \times 10^9/L$, chemotherapy will be interrupted until recovery. When patients have grade 4 haematological toxicity, impaired renal function and other non-haematological toxicities, the dose of docetaxel and nedaplatin will be reduced. If adjuvant chemotherapy is postponed for > 4 weeks, the patient will be suspended from subsequent chemotherapy but will continue to complete the follow-up schedule.

For all patients on both arms, an assessment will be conducted by the treating physician every 3 months for the first 2 years, then 6 monthly until 5 years, then yearly thereafter. During each scheduled visit, physical examination (including body weight and PS, vagino-recto-abdominal

examination), tumour biomarker tests, HPV DNA test and documentation of the status of inguinal and supraclavicular lymph nodes will be performed. Thin-cytologic test, colour Doppler of supraclavicular and inguinal lymph nodes, chest CT, abdominal and pelvic MRI and bone scan will be required at 6, 12, 18 and 24 months and then yearly post-chemotherapy. Evaluation of late toxicity (defined as toxicity that occurs at least 3 months after the last day of RT) of the gastrointestinal tract, rectum, kidneys and bladder and lymphoedema will be performed at each visit using the Radiation Therapy Oncology Group and European Organisation for Research and Treatment of Cancer late radiation morbidity scoring criteria.³⁶

Data collection and management

Every participant will be assigned a unique trial number on consenting to the study and identified in all study-related documentation by the trial number and initials.

Participating centres' completed case report forms (CRFs) consist of the following:

1. Eligibility checklist before or at the time of randomisation.
2. Pretreatment and tumour assessment at baseline prior to RT or CRT. The collected data included histology, FIGO stage, tumour size, lymph status, HPV type, tumour biomarker and RT sheet (including the total dose and fraction of RT and brachytherapy, regimen and cycle of concurrent chemotherapy).
3. Treatment forms on day 1 of each chemotherapy cycle. The collected data included PS, baseline laboratory tests, protocol treatments received, toxicity and reasons for reduction/delay/omission of treatment.
4. Toxicity forms that will be completed weekly of each cycle of chemotherapy.
5. Follow-up forms at each follow-up visit. The collected data included late toxicities, serious adverse events and patient's status (progression/relapse/death).

Copies of all CRFs will be returned to the trial centre for statistical analysis. Paper copies of the CRFs will be retained at sites for at least 15 years following the last

patient entered. All data will be uploaded to a study-defined database.

The trial centre sponsors will be in regular contact with local centre personnel to check on the progress and help with any question that may arise. Incoming forms will be checked for completeness, consistency, timeliness and compliance with the protocol.

Planned statistical analyses

Intention-to-treat analyses will be performed for survival, and a Kaplan-Meier survival curve will be used to analyse all time-to-event data. A log-rank test will be used to estimate the difference in survival between the two patient groups. The HR and 95% CI will be assessed using Cox proportional hazards model. Missing data will be censored at the date they are last known to be alive. Adverse events (grades 3 to 5) will be compared between groups using χ^2 of Fisher's exact test for the safety population (defined as patients who received at least one dose of chemotherapy). All tests will be two-sided, and a p value of 0.05 will be considered statistically significant.

Patient and public involvement statement

The patients and public are not involved in the design and conduct of the study.

ETHICS AND DISSEMINATION

All investigators shall comply with the protocol, unless a protocol amendment needs to eliminate immediate hazard to a participant. Data from all centres will be analysed together and reported as soon as possible. Individual participants cannot publish data about their patients that are directly related to questions proposed by the trial until the Trial Management Group (TMG) has published its report. The TMG will have access to the final data set, form the basis of the Writing Committee and advise on the nature of publications. With regard to dissemination, the results of this study will be published in an academic journal and presented at national and international conferences.

DISCUSSION AND CONCLUSION

There is growing evidence supporting that patients with cervical cancer with persistent HPV DNA post-RT have increased recurrence than those without. There are also no definitive data on the group that will benefit from adjuvant chemotherapy. This presented randomised trial evaluated for the first time whether adjuvant chemotherapy post-RT in cervical cancer with residual HPV DNA can result in higher tumour control rates compared with clinical surveillance only. The study is currently recruiting participants. The study opened the recruitment in China on 1 March, 2018, the first patient was enrolled on 19 August, 2018, and 10 eligible patients have been enrolled.

Author affiliations

¹Radiotherapy Department, The Second Affiliated Hospital of Fujian Medical University, Quanzhou, China

²Radiotherapy Department, Sun Yat-sen University Cancer Center, Guangzhou, China

³Gynecology Department, Fujian Provincial Tumor Hospital, Fuzhou, China

Contributors YHW and YOY drafted the main manuscript. JJS and JL did the literature search. QRC played a chief role in statistical part. YHW, QX, ZGB and XPC participated in the design of the study. All authors have read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethics approval for this trial has been granted by the Ethics Committee of the Second Affiliated Hospital of Fujian Medical University on 6 February, 2018, (No.28).

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iD

Yanhong Wang <http://orcid.org/0000-0001-8152-0574>

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