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RESEARCH ARTICLE

Adjuvant chemotherapy versus adjuvant concurrent chemoradiotherapy after radical surgery for early-stage cervical cancer: a randomized, non-inferiority, multicenter trial

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Abstract **We conducted a prospective study to assess the non-inferiority of adjuvant chemotherapy alone versus adjuvant concurrent chemoradiotherapy (CCRT) as an alternative strategy for patients with early-stage (FIGO 2009 stage IB–IIA) cervical cancer having risk factors after surgery. The condition was assessed in terms of prognosis, adverse effects, and quality of life. This randomized trial involved nine centers across China. Eligible patients were randomized to receive adjuvant chemotherapy or CCRT after surgery. The primary end-point was progression-free survival (PFS). From December 2012 to December 2014, 337 patients were subjected to randomization. Final analysis included 329 patients, including 165 in the adjuvant chemotherapy group and 164 in the adjuvant CCRT group. The median follow-up was 72.1 months. The three-year PFS rates were both 91.9%, and the five-year OS was 90.6% versus 90.0% in adjuvant chemotherapy and CCRT groups, respectively. No significant differences were observed in the PFS or OS between groups. The adjusted HR for PFS was 0.854 (95% confidence interval 0.415–1.757; *P* = 0.667) favoring adjuvant chemotherapy, excluding the predefined non-inferiority boundary of 1.9. The chemotherapy group showed a tendency toward good quality of life. In comparison with post-operative adjuvant CCRT, adjuvant chemotherapy treatment showed non-inferior efficacy**

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in patients with early-stage cervical cancer having pathological risk factors. Adjuvant chemotherapy alone is a favorable alternative post-operative treatment.

Keywords chemotherapy; cervical cancer; lymph node metastasis; concurrent chemoradiotherapy; quality of life

Introduction

Despite significant advances in HPV vaccine development and cervical dysplasia screening and treatment, cervical cancer remains the fourth most common cancer in women and the third leading cause of cancer-related mortality among women worldwide. An overall profile of patients with cervical cancer in China in 2013 revealed an average age of 44.7 years at diagnosis, which is 5–10 years younger than the average ages reported before 2000 [1]. Cervical cancer is among the most common cancers diagnosed in female patients under the age of 40 years. The increased proportion of younger patients and earlier disease stage has increased the emphasis on preserving genital and endocrine functions and survival benefits.

Based on National Comprehensive Cancer Network (NCCN) guidelines, radical hysterectomy and pelvic lymph node dissection are typical treatments for early-stage cervical cancer. For patients with surgical-pathological risk factors, concurrent chemoradiotherapy (CCRT) is recommended as standard adjuvant therapy after surgery, and this treatment reduces recurrence and improves prognosis [2]. Long-term survivors show an increased incidence of complications and poor sexual function caused by the impairment of organs and tissues in the pelvic including ovary by radiation [3]. Therefore, an effective adjuvant treatment without radiation is urgently needed, particularly for young patients with cervical cancer. Platinum-based combination regimens were reported as adjuvant chemotherapy for the treatment of patients with cervical cancer having risk factors and displayed positive results in some retrospective studies with relatively small patient cohort [4–8]. The favorable results warrant the performance of a prospective randomized trial, in which adjuvant chemotherapy alone was carried out for patients with cervical cancer after radical hysterectomy.

We conducted a prospective, randomized, multicenter, non-inferiority clinical trial in patients with stage IB-IIA cervical cancer having surgical-pathologic risk factors. The patients received either adjuvant chemotherapy of combined cisplatin and paclitaxel or standard adjuvant CCRT. Careful assessment was made for the prognosis, adverse effects, and quality of life to evaluate the potential use of adjuvant chemotherapy alone as an alternative strategy for patients with early-stage cervical cancer.

Methods

Patients

This prospective, randomized, non-inferiority trial of combination chemotherapy of paclitaxel and cisplatin versus CCRT for postoperative cervical cancer patients with risk factors was designed and overseen by Southeast-middle China Gynecological Oncology Group (CSEM-GOG) and was performed at nine hospitals in Chinese mainland. All participating institutions obtained local ethics approval, and this trial was registered with ClinicalTrials.gov (NCT01755897). All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000. Informed consent was obtained from all patients for inclusion in the study.

All included patients were 18–65 years of age, had stage IB–IIA squamous cell carcinoma of the uterine cervix according to the staging system of the International Federation of Gynecology and Obstetrics (FIGO 2009), and received radical hysterectomy and pelvic and/or paraaortic lymphadenectomy as primary treatment. Ovarian transposition was performed to protect ovary function on a voluntary basis. Pathologic risk factors were confirmed as the indication of adjuvant therapy, such as lymph node metastasis (LNM), positive parametrial invasion (PMI), deep stromal invasion (DSI), histopathological grading indicating poor differentiation (G2–G3), lymphatic vascular space involvement (LVSI), or bulky tumor (BT, tumor diameter > 4 cm). Patients suffering from severe or uncontrolled internal disease, unable to receive surgery, and/or unsuitable for radiotherapy or chemotherapy were excluded. All enrolled patients provided written informed consents.

Procedures

After surgery, eligible patients with confirmed histopathological characteristics were randomly assigned in a 1:1 ratio to receive either combination chemotherapy or CCRT according to the randomization sequence generated by computer kept in the primary investigation institution, and the patients were stratified by each branch institution. The investigators were not masked to the patients' allocated treatment, and the patients were aware of their group assignment. Case report forms were

finished by investigators in each hospital under the supervision of the primary investigation institution.

In the adjuvant chemotherapy group, 135–175 mg/m^2 paclitaxel and 75–80 mg/m^2 (TP) cisplatin were intravenously administered at intervals of 3–4 weeks beginning 3–4 weeks after surgery. Three cycles of TP therapy were administered in patients with only one of the following risk factors: DSI, G2–G3, LVSI, or BT [9]. Six cycles of TP therapy were administered in patients with pelvic LNM and/or PMI, or with two or more risk factors [10]. In the adjuvant CCRT group, patients received external beam radiation therapy (45–50.4 Gy/4–7 weeks) with IV injection of 35–40 mg/m^2 cisplatin once a week [11]. Patients with BT or vaginal cutoff less than 3 cm received brachytherapy. The total treatment duration was 6–7 weeks. All patients underwent follow-up assessment every 3 months during the first 2 years follow-up and every 6 months until the end of follow-up.

Outcomes

The primary endpoint was progression-free survival (PFS), which was defined as the period of randomization until the event (progression confirmed either radiologically or clinically if scan not performed or death from any cause) happened or until the patient was censored at the date of follow-up. Secondary endpoints included the overall survival (OS) and the assessment of treatment-related toxicity and quality of life. Overall survival was defined as the period of time from randomization to death from any cause and was censored during the final confirmation of survival for surviving patients, or during the final confirmation of survival before being lost to follow-up for patients lost to follow-up. Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Health-related quality of life was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30, version 3.0) and the cervix 24 module (CX24). Higher scores on functional and global health-related quality of life scales represent good levels of functioning. On the symptom subscales, higher scores reflect higher levels of symptoms. Follicle-stimulating hormone (FSH) and estradiol (E2) were measured to evaluate the ovarian function and symptoms of menopause, including hot-flash and vaginal atrophy. Recurrence site was classified as local if it is within the pelvic field and locoregional if it is within the vagina, para-aortic lymph nodes, or abdomen; otherwise, it was classified as distant.

Statistical analysis

All analyses were performed on an intention-to-treat basis, except for a sensitivity analysis that was performed according to per-protocol treatment. The expected three-year was approximately 90% with post-operative adjuvant CCRT in FIGO IB-IIA cervical cancer patients with risk factors for relapse [2,12–14]. Considering the differences of PFS noted in previous trials and clinical consensus [15–17], we defined the lower boundary of the interval of between-group difference as 8.5%; to show non-inferiority, we set the upper bound of the hazard ratio (HR) to be less than 1.9. A total of 326 patients were required for two-year enrollment and five-year follow-up, allowing for 10% treatment switch and withdrawal cases, with a 5% two-sided type I error rate and 80% power.

The baseline characteristics were compared between two groups by using Chi-square and Mann–Whitney U test. Kaplan–Meier curves were compared using the log-rank test. The Cox hazard regression model was used to identify the risk factors associated with PFS or OS. Cox regression models were used to calculate treatment HR with a 95% confidence interval (CI). HR < 1 indicated that combination chemotherapy is beneficial. FSH > 25 mIU/mL indicates premature ovarian insufficiency (POI), while FSH > 45 mIU/mL indicates menopause. All *P* values were two-sided. Adverse events were reported until 12 months after treatment had been administered. Changes in health-related quality of life were evaluated using linear or ordinal logistic mixed model. Data were analyzed using SAS statistical software (version 9.4 for Windows, SAS).

Results

Patients

A total of 337 patients were recruited at nine medical centers from December 2012 through December 2014. Baseline characteristics are shown in Table 1. After randomization, one patient was found not to meet the inclusion criteria, two patients chose traditional Chinese medicine, four patients changed their mind and refused any postoperative adjuvant therapy, and one patient refused to follow-up after finishing adjuvant treatment. Finally, 329 women were included in the intention-to-treat (ITT) population (Fig. 1 and Table S1), including 165 in the adjuvant chemotherapy group and 164 in the adjuvant CCRT group.

Treatment

The median duration between surgery and adjuvant therapy was 24 days (IQR 15.0–35.0). The proportion of patients who completed the entire treatment protocol was 91.1% in the three-cycle group and 53.0% in the six-cycle group. The average dose of paclitaxel was 168.7 ± 5.3 mg/m^2, and the average dose of cisplatin was 76.8 ±

Table 1 Baseline characteristics of 337 patients

Variable	Adjuvant CT group (N = 166)	Adjuvant CCRT group (N = 171)
Age at randomization (year)		
Range	24−64	27−60
Average	45.8 ± 8.5	46.5 ± 7.5
⩽ 40 (n (%))	44 (26.5)	41 (24.0)
41–50 (n (%))	70 (42.2)	68 (39.8)
>50 (n (%))	52 (31.3)	62 (36.2)
FIGO stage (n (%))		
IB1	83 (50.0)	88 (51.5)
IB2	44 (26.5)	46 (26.9)
IIA1	27 (16.3)	26 (15.2)
IIA2	12 (7.2)	11 (6.4)
Deep stromal invasion (n (%))	91 (54.8)	101 (59.1)
Histopathological grade G2−G3 (n (%))	76 (45.8)	73 (42.7)
Lymphatic vascular space involvement (n (%))	41 (24.7)	35 (20.5)
Diameter (mm, average)	26.4 ± 11.9	26.6 ± 12.2
Lymph node metastasis (n (%))	30 (18.1)	36 (21.1)
Sigle positive node (n)	17	19
Multiple positive nodes (⩾ 2) (n)	13	17
Positive parametrial invasion (n (%))	5 (3.0)	4 (2.3)
Single risk factor w/o LNM or PMI (n (%))	78 (47.0)	76 (44.4)
Multiple risk factors or LNM or PMI (n (%))	88 (53.0)	95 (55.6)
Ovarian conservation (n (%))	66 (39.6)	63 (36.8)
Initial SCCA (ng/mL, median)	1.52	1.70
Intention-to-treat population (n (%))	165 (99.4)	164 (95.9)
Per-protocol population (n (%))	152 (91.6)	144 (84.2)

Abbreviations: CT, chemotherapy; CCRT, concurrent chemoradiotherapy; FIGO, International Federation of Gynecology and Obstetrics; LNM, lymph node metastasis; PMI, positive parametrial invasion; SCCA, squamous cell carcinoma antigen.

2.6 mg/m^2. In the adjuvant CCRT group, all patients underwent both irradiation and concurrent chemotherapy. Approximately 90.0% of the patients completed at least three cycles of concurrent chemotherapy, and the median cycle number of concurrent cisplatin therapy was 4 (range: 1–5). The average dose of cisplatin was 37.2 ± 1.9 mg/m^2. Regimen doses were well tolerated. Among the 329 patients in the ITT population, 296 patients were included in the per-protocol population at analysis. The pre-determined plan was changed in 13 patients in adjuvant chemotherapy group (13/165, 7.8%) and 20 in the adjuvant CCRT group (20/164, 12.2%).

Efficacy

By December 31, 2019, 31 PFS events (15 in adjuvant chemotherapy group and 16 in adjuvant CCRT group) occurred among ITT population, and the median duration of follow-up was 72.1 months. The three-year PFS rate were both 91.9% in the adjuvant chemotherapy and adjuvant CCRT groups, while the five-year PFS rates were 90.6% and 90.0%, respectively (unadjusted HR, 0.933; 95% CI 0.461–1.887; P = 0.846). PFS did not significantly differ between the two groups. After adjusted in terms of age, LNM and PMI were determined using multivariable analysis of risk factors, and no significant difference in PFS was found between the two groups (adjusted HR, 0.854, 95% CI 0.415–1.757, P = 0.667; Fig. 2A and Table S3). The upper bound of the HR level was below the boundary of 1.9, indicating non-inferiority for this study. In the per-protocol population, PFS demonstrated a non-inferiority result (Fig. S1 and Table S2). Estimation of overall survival did not reveal significant differences between the two groups. The three-year and five-year OS rates were 95.6% and 93.7% in adjuvant chemotherapy group versus 95.6% and 92.4% in adjuvant CCRT group (adjusted HR, 0.673; 95% CI 0.277–1.640, P = 0.384, Fig. 2B and Table S2).

In both groups, the most common recurrence sites were local and locoregional. One patient in adjuvant

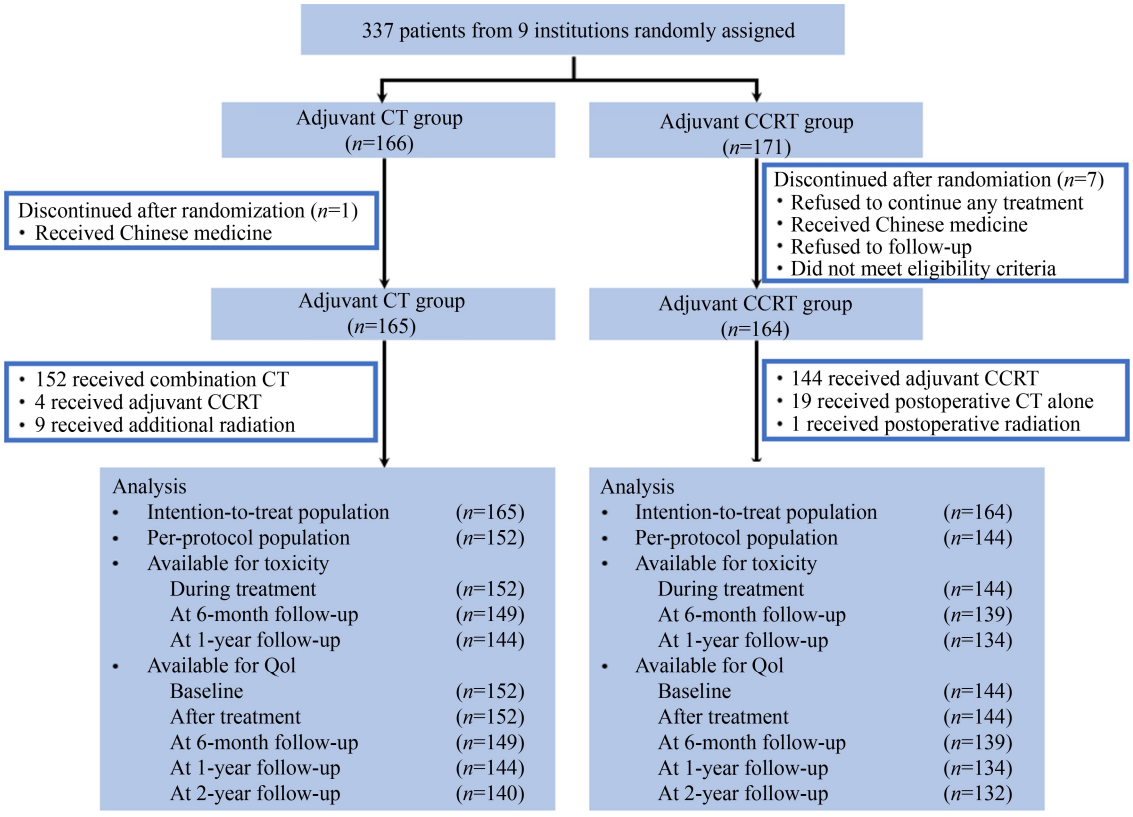

Fig. 1 CONSORT diagram. CT, chemotherapy; CCRT, concurrent chemoradiotherapy.

chemotherapy group presented distant recurrence in mediastinal lymph node and upper suraclavicular lymph node. Five patients in adjuvant CCRT group were confirmed with distant recurrence with lung metastasis in two cases, supraclavicular node involvement in two cases, and both lung metastasis and intercostal lymph node involvement in one case. No significant difference was observed between the two groups (Fisher's exact $P = 0.288$, Table 2). A total of 22 patients died. Ten patients in adjuvant chemotherapy group and 11 patients in the adjuvant CCRT group died from cervical cancer. One patient in the adjuvant CCRT group died from rectum cancer without cervical cancer recurrence, as confirmed by post-operative pathology.

The evaluation of subgroup analyses for treatment efficacy by single risk factor, multiple risk factors, and LNM or PMI on PFS and OS are shown in Figs. 3 and 4. Among the patients with LNM and/or PMI, PFS and OS rates were moderately higher in adjuvant chemotherapy group, but they did not remarkably differ from those in the adjuvant CCRT group. No significant differences in treatment efficacy was observed in the single risk factors, such as G2–G3 and DSI (Figs. S2 and S3, Table S5). A total of 79 patients met the Sedlis criteria, patients who received adjuvant CCRT showed high PFS and OS, and no substantial difference was found between treatments (Fig. S4, Tables S4 and S5).

Toxicity

A total of 22 patients exhibited lower-limb lymphedema after radical hysterectomy, and all patients recovered within 3 months. Bladder dysfunction, including incomplete bladder emptying and straining to micturate, occurred in 56% (185/329) patients, in which complete bladder emptying occurred after a median of 12 days (range, 7–118 days). No patient experienced grade 4 hypersensitivity reactions resulting from chemotherapy. Grade 3–4 myelotoxicity was slightly more frequent among patients in the 6-cycle chemotherapy group ($P < 0.001$ vs. three-cycle chemotherapy group; $P < 0.001$ vs. CCRT group). Radiation-related proctitis, cystitis, and dermatitis were the most common complications among patients in the CCRT group. Colonoscopy revealed proctitis in six patients with long-standing bowel complications at 24 months after treatment in CCRT group. Cystoscopy revealed cystitis in five patients in adjuvant chemotherapy group and 11 in CCRT group at 2–3 years after treatment. The frequency of toxicity was shown in Table S6.

Quality of life

During the two-year follow-up period, the EORTC-Q30 scores decreased after surgery and adjuvant treatments,

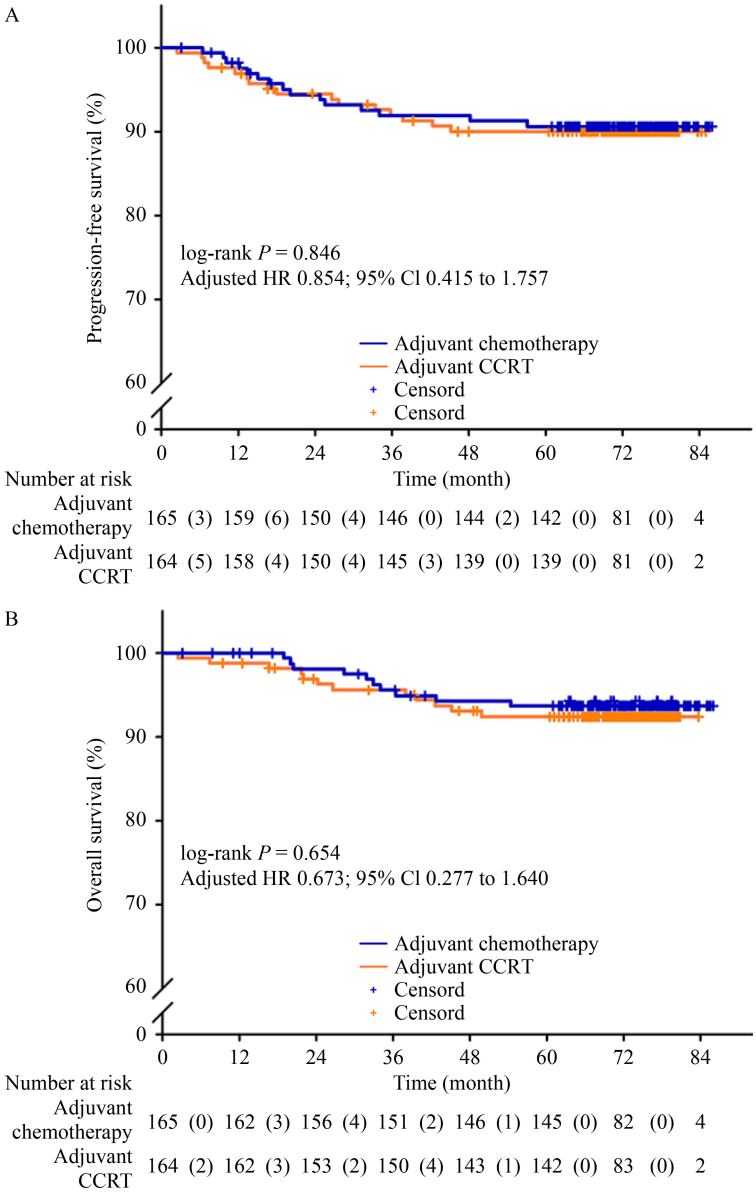

Fig. 2 Progression-free survival (PFS) and overall survival (OS) in the intent-to-treat population. Kaplan–Meier plots for (A) PFS and (B) OS in the intent-to-treat population by treatment group: adjuvant chemotherapy group and adjuvant CCRT group. The three-year PFS rates were both 91.9%, and the five-year PFS was 90.6% versus 90.0%, respectively in adjuvant chemotherapy and adjuvant CCRT groups. The HR for PFS excluding the predefined non-inferiority boundary of 1.9, demonstrating a significant non-inferiority. Estimated OS was similar to the PFS. Numbers in parentheses represent the number of events (deaths or progressions) between the two time points.

Table 2 Recurrence and death patterns

Treatment group	Adjuvant CT group ($N = 15$)	Adjuvant CCRT group ($N = 15$)	P value
Recurrence (n)			0.288
Local	8	4	
Locoregional	6	6	
Distant	1	5	
Death (n)	10	12[a]	

Abbreviations: CT, chemotherapy; CCRT, concurrent chemoradiotherapy.
[a]One patient in adjuvant CCRT group died from rectum cancer without cervical cancer recurrence, as confirmed by postoperative pathology.

and then recovered gradually, and no difference was observed between the two treatments, except for the temporary diarrhea caused by radiation (Table S7). An obvious severity of cervical cancer-related symptoms was observed in patients who received CCRT. Menopausal symptom and sexual worry persisted significantly worse in adjuvant CCRT group than the adjuvant chemotherapy group over the two-year follow-up ($P < 0.001$ for menopausal symptom, $P = 0.002$ for sexual worry).

Ovarian transposition was performed in 129 patients. Ovarian function was evaluated in 82 patients at 36

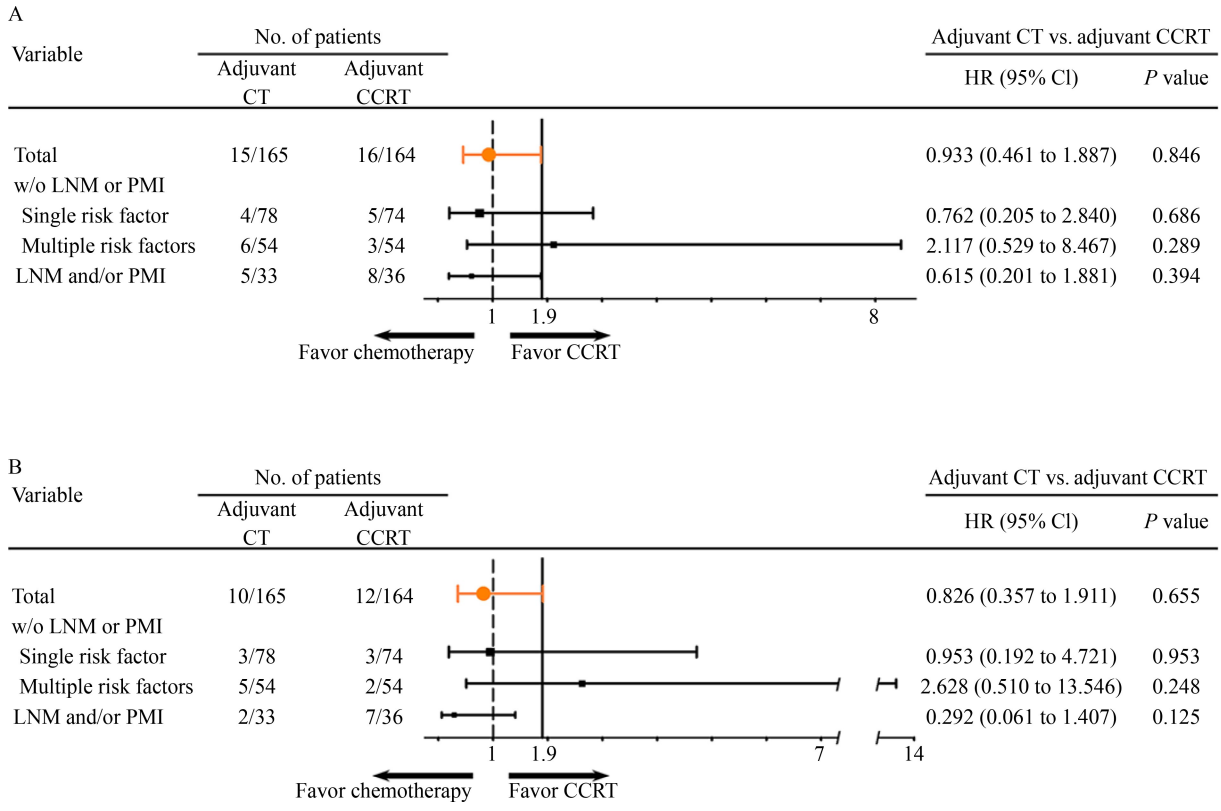

Fig. 3 Subset analysis by using Cox regression model displayed in a forest plot and plotted on the log scale with 95% CI. (A) Progression-free survival (PFS) and (B) overall survival (OS). Horizontal lines represent hazard ratios (HRs; with 95% CIs). Treatment interaction was assessed using a multivariate Cox proportional model. The HRs are relative to the adjuvant CCRT group and vary at approximately 1.0. The vertical line at 1.0 represents no difference in the HRs; HR < 1 favors adjuvant chemotherapy and HR > 1 favors adjuvant CCRT. The vertical line at 1.9 represents upper bound of the hazard ratio. CT, chemotherapy; CCRT, concurrent chemoradiotherapy; CI, confidence interval; LNM, lymph node metastasis; PMI, positive parametrial invasion. Single risk factor including DSI (deep stromal invasion), G2 to G3 (histopathological grading indicating poor differentiation), LVSI (lymphatic vascular space involvement), bulky tumor (tumor diameter > 4 cm). Multiple risk factors including two or more of the risk factors in single risk factor group.

months after treatment. The patients in CCRT group presented relatively high FSH and low E2 levels, which significantly differed from the levels in adjuvant chemotherapy group (Fig. 5, $P = 0.002$ for FSH and $P = 0.004$ for E2, calculated by Mann–Whitney U test). Objective examination results revealed that hot flashes and vaginal atrophy frequently occurred among patients in the CCRT group ($P = 0.002$ for hot flashes; $P < 0.001$ for vaginal atrophy), suggesting that radiation commonly leads to ovarian damage ($P = 0.028$ for POI; $P = 0.027$ for menopause, Table S8). Ovarian metastasis was not observed in patients throughout the follow-up.

Discussion

Although patients with early-stage cervical cancer have a good prognosis, nearly half of the patients have prognostic risk factors and need adjuvant treatment after primary radical hysterectomy and pelvic lymph node dissection [18]. However, information about the risk factor and indication of adjuvant therapy varies across different guidelines. For example, patients with either intermediate- or high-risk factor and without a contraindication for cisplatin are recommended for CCRT based on the German Gynecological Oncology Group (AGO) guideline. However, based on the NCCN guideline, patients with intermediate-risk factors according to Sedlis criteria undergo radiotherapy alone, and patients with high-risk factors undergo CCRT. Adjuvant chemotherapy alone or observation with omitting radiotherapy could be used even with high-risk-factors in Korean Society of Gynecologic Oncology Consensus Statement. Retrospective studies and literature reviews have focused on the efficacy of post-operative adjuvant treatments, but considering the lack of evidence from randomized clinical trials, treatment remains unclear for the survival benefit of different adjuvant treatment.

Radiotherapy remarkably improves the prognosis of patients [19]. Based on the comparison of the efficacy of CCRT with RT in early-stage cervical cancer patients who received surgery, the adjuvant CCRT showed superior efficacy over RT in patients with intermediate- or

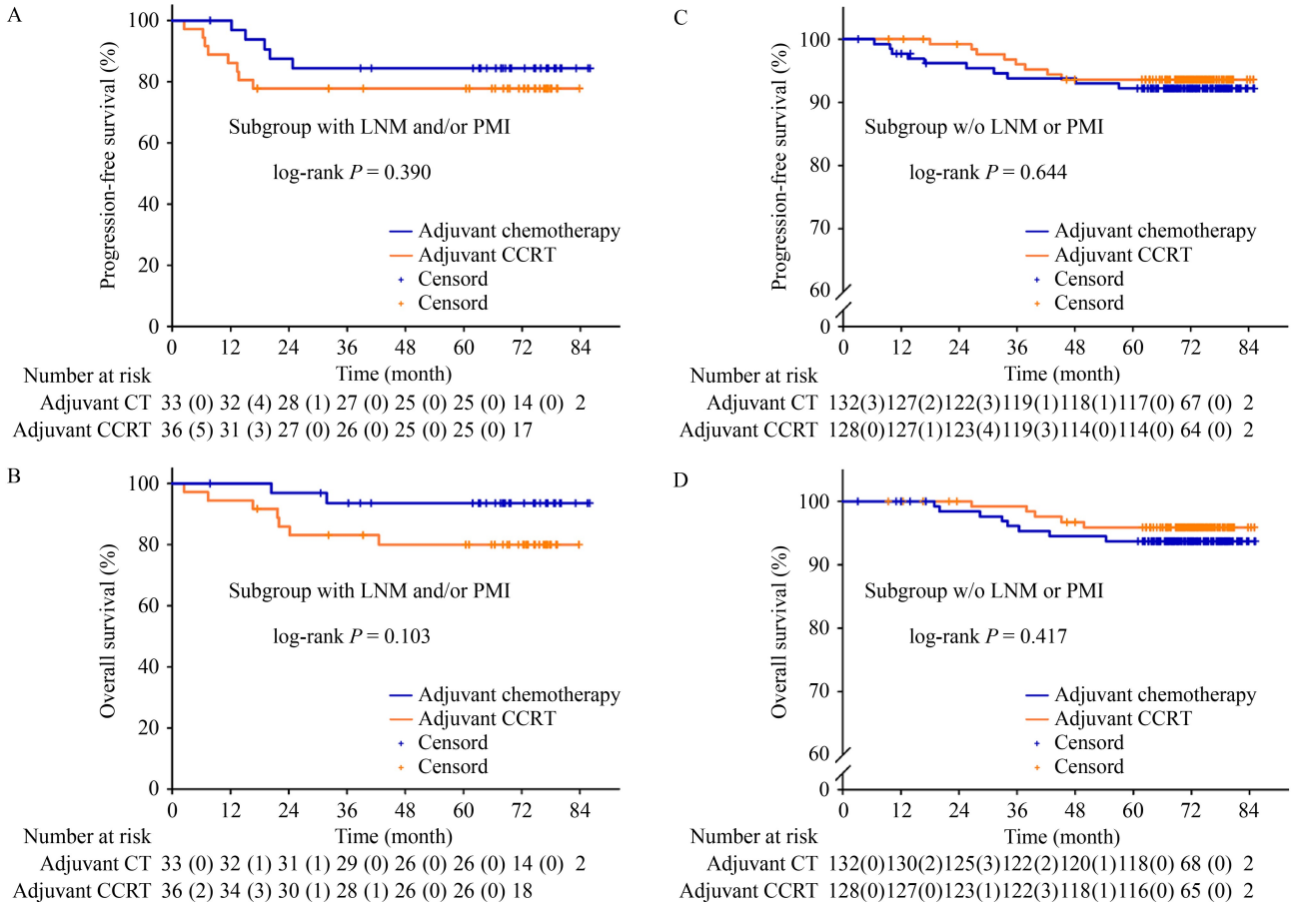

Fig. 4 Progression-free survival (PFS) and overall survival (OS) in subgroups. Kaplan–Meier plots for (A) PFS and (B) OS in the group with lymph node metastasis and/or positive parametrial invasion; no significant differences in PSF and OS were observed between the two treatment groups; log-rank $P = 0.390$ for PFS; log-rank $P = 0.103$ for OS. (C) PFS and (D) OS in the group without lymph node metastasis or positive parametrial invasion; no significant differences in PSF and OS were observed between the two treatment groups; log-rank $P = 0.644$ for PFS; log-rank $P = 0.417$ for OS. Numbers in parentheses represent the number of events (deaths or progressions) between the two time points. CT, chemotherapy; CCRT, concurrent chemoradiotherapy.

high-risk factors [20]. However, the disadvantage includes the additional physical disorders during treatment, including abdominal distension, painful bladder neuropathy, and anorectal dysfunction. Moreover, radiation can induce irreversible ovarian damage, leading to premature menopause and sexual dysfunction [3,21–23], which remarkably affects the quality of life.

Chemotherapy is primarily used as a radiation sensitizer in concurrent chemoradiotherapy, for the treatment of advanced and recurrent diseases, or as the neoadjuvant treatment for local advanced cervical cancer. Generally, cervical cancer is not believed to be a chemosensitive tumor. The cancer is actually chemosensitive, but the usage of regimen containing cisplatin is limited in the patients with adequate renal function [24]. Several retrospective studies showed the benefit of chemotherapy alone as adjuvant therapy after radical hysterectomy. Only Jung *et al*. retrospectively analyzed 262 patients with FIGO stage IB–IIA cervical cancer and concluded that the therapeutic effect of chemotherapy alone was non-inferior to that of adjuvant radiotherapy or concurrent chemoradiation therapy, and chemotherapy results in long-term complications [25]. In 2018, Matsuo *et al*. published a retrospective study to assess the effectiveness of adjuvant chemotherapy following radical hysterectomy for patients with intermediated-risk stage IB cervical cancer. A total of 555 women were included in the intermediate-risk group (DSI > 50%, large tumor size > 4 cm, and LVSI), 223 patients received chemotherapy alone, 172 patients received CCRT, and 160 patients received radiotherapy. The five-year disease-free survival rates were similar across the adjuvant therapy groups [26]. Our clinical trial, to our knowledge, is the first randomized, non-inferiority, multicenter clinical trial of comparison between combined chemotherapy with CCRT as a postoperative adjuvant therapy for patients with stage IB–IIA cervical cancer having risk factors. We introduced a concise indication for the postoperative adjuvant therapy. The results in this study showed that postoperative adjuvant chemotherapy alone resulted in a

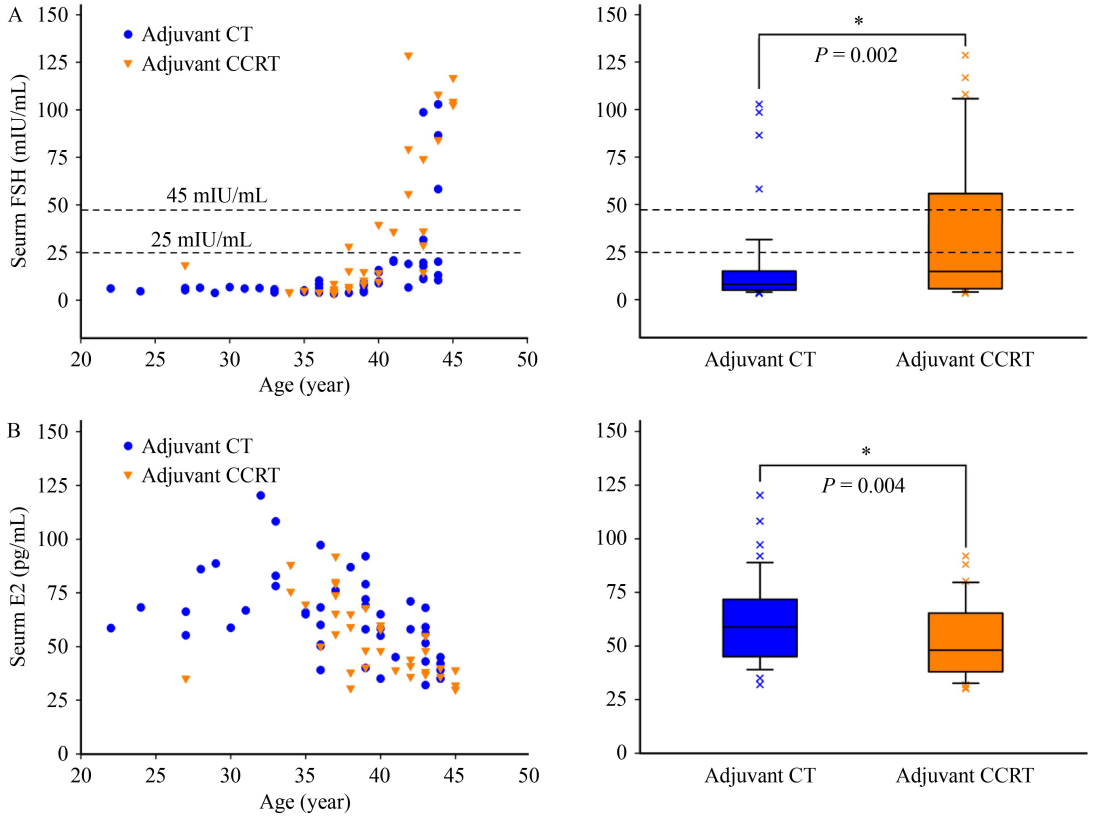

Fig. 5 Serum FSH and E2 at 36 months after randomization. Data from 82 patients whose ovarian function were evaluated at 36 months after randomization. Higher FSH level (A) and lower E2 level (B) in adjuvant CCRT group were significantly different from adjuvant chemotherapy group ($P = 0.002$ for FSH and $P = 0.004$ for E2). FSH > 25 mIU/mL refers to premature ovarian insufficiency (POI), FSH > 45 mIU/mL refers to menopause. Right panels indicated the median (line in the box), interquartile range (box), 90% confidence intervals (error bar), and all the outliers.

similar efficacy when compared with patients in adjuvant CCRT group and resulted in non-inferiority of PFS. Chemotherapy tends to inhibit distant metastasis [7], but other studies showed no differences [26]. In our study, only one case had distant metastases in the adjuvant chemotherapy group and five in adjuvant CCRT group. However, effective statistical analysis could not be performed because of the insufficient number of cases.

The risk factors in the guidelines worldwide slightly differ. For instance, positive surgical margin is not included in the high-risk factors in the Japanese guidelines. In the present study, histologic low grade is a risk factor associated with the application of adjuvant treatment. In the Gynecologic Oncology Group (GOG) study of clinical and pathologic predictors of surgically treated FIGO stage I cervical cancer published in 1990, histologic grade was identified as linearly correlated with disease-free interval (DFI), but it was not an independent prognostic factor for DFI [27]. In the present study, positive pelvic lymph node influenced DFI but not survival. Based on the accumulation of clinical evidence, lymph node metastasis is a widely accepted high-risk factor. Our latest study that includes 4220 cervical cancer cases found that seven independent risk factors, including histologic grade, were associated with patient outcome. Some of the reasons for this difference include the following: (1) none of the recent studies evaluated the influence of the risk factor of the outcome on the manner of single risk factor alone. Most of the patients had a different combination of risk factors. Consequently, the analysis became more complicated, adequate case numbers were lacking; (2) the mix of outcomes of patients who received different adjuvant treatment could influence the results of statistics analysis; and (3) the adjuvant treatment changed from time to time. Lack of high quality of evidence for adjuvant treatment and the requirements from patients for both benefit of survival and quality of life require that a treatment choice is developed.

In the subgroup analysis of our study, 38 patients who met the Sedlis criteria and received adjuvant chemotherapy had a lower three-year PFS rate of 86.0% (94.9% in adjuvant CCRT arm, log-rank $P = 0.208$). In comparison with the two-year recurrence-free of the radiation treatment in the GOG 92 study (88%) [19], the adjuvant chemotherapy showed acceptable survival benefit. Although the deficiency of the post hoc analysis made the results less powerful, the adjuvant chemotherapy or

CCRT could be a good choice for the patients who had postoperative pathologic risk factors.

Chemotherapy is harmful to ovarian function, the extent of damage depends on the type and dose of the agents used, and the number of treatment cycles. Based on the comparison of alkylating agents, cisplatin and paclitaxel induce relatively slight and transient ovary injury. In the present current study, patients underwent three or six cycles of TP therapy according to the risk factors, and most of patients tolerated the TP regimen. A total of 129 patients underwent ovary-conserving operations, and no ovary metastases were detected in these patients. This finding is consistent with prior data showing extremely low rates of ovarian metastasis in cervical cancer patients [16,28].

The study has some limitations. We enrolled patients with different risk factors, including LNM or PMI, and referred to high-risk factors. Moreover, we did not stratify the patients according to clinical stages or risk factors. Some patients violated the original treatment protocol during treatment and follow-up. Nevertheless, the efficacy analysis results did not differ between the ITT population and the per-protocol population. Moreover, the PFS and OS event rates were lower than expected, and the subset analysis cannot reveal the detailed characteristic of the patients who benefited from the post-operative chemotherapy alone. However, our study was designed to assess the time-based result of three-year PFS and the QOL and OS at a less follow-up time of 5 years (60 months after having recruited the last patient) other than event-based. We achieved non-inferiority with analysis at a median follow-up of 6 years. The major strengths of this study include its multi-center nature, moderate length of follow-up, and detailed collection of side-effect data.

In summary, the present prospective study was performed in a population of IB–IIA squamous cell cervical cancer patients with surgical-pathological risk factors. The patients randomized to receive either combination chemotherapy or CCRT did not significantly differ in the primary end point of PFS or the secondary end point of OS. Furthermore, patients receiving combination chemotherapy showed benefits such as good quality of life and ovarian function maintenance. Our results have important implications for clinical practice for patients who also benefit from lower treatment costs of chemotherapy and its use in remote areas where radiotherapy equipment is lack. We realized the advantage of chemotherapy treatment with 3–4 weeks interval in these unprecedented times of COVID-19 to protect patients from frequent hospital visits and then reducing their risk of infection. Larger sample size and long-term observation should be employed in further studies to determine which subset of patients will benefit the most.

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Compliance with ethics guidelines

Danhui Weng, Huihua Xiong, Changkun Zhu, Xiaoyun Wan, Yaxia Chen, Xinyu Wang, Youzhong Zhang, Jie Jiang, Xi Zhang, Qinglei Gao, Gang Chen, Hui Xing, Changyu Wang, Kezhen Li, Yaheng Chen, Yuyan Mao, Dongxiao Hu, Zimin Pan, Qingqin Chen, Baoxia Cui, Kun Song, Cunjian Yi, Guangcai Peng, Xiaobing Han, Ruifang An, Liangsheng Fan, Wei Wang, Tingchuan Xiong, Yile Chen, Zhenzi Tang, Lin Li, Xingsheng Yang, Xiaodong Cheng, Weiguo Lu, Hui Wang, Beihua Kong, Xing Xie, and Ding Ma have no conflict of interest. All participating institutions obtained local ethics approval, and this trial was registered with ClinicalTrials.gov (NCT01755897). All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000. Informed consent was obtained from all patients for inclusion in the study.

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