Journal of Cancer Treatment and Research
2025, Vol. 13, No. 3, pp. 83-90
https://doi.org/10.11648/j.jctr.20251303.16

Research Article

Localised Cervical Cancer: Impact of Weekly Chemotherapy and Postoperative Radiotherapy in Chinese Women

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Abstract

Introduction: recurrence after treatment for uterine cervical cancer is not uncommon, and its management is a major challenge for the clinician. The aim of this study was to determine the maximum tolerated dose and dose-limiting toxicity of weekly chemotherapy combined with postoperative radiotherapy for uterine cervical cancer. *Material and methods*: Chinese women with localised uterine cervical cancer were recruited between 2017 and 2020. Pelvic radiotherapy (6 -10 MV X-rays, IMRT 40-45 Gy / 20 fractions, boost of 10-20 Gy/ 5-10fractions on parameters) was followed by brachytherapy (^{192}Ir, 10 - 20Gy/2-4fractions). Weekly chemotherapy was initiated with 20 mg/m^2 cisplatin and 10mg/m^2 paclitaxel. The 5 + 5 approach to escalate the dose for each 5 patients until the dose-limiting toxicity level was reached was used. *Results*: a total of 30 patients aged 32-78 years were included. Two out of 5 patients in the dose level 5 group developed grade 3 diarrhoea after 4 weeks. One patient in dose level 4 and 6 developed grade 4 leukopenia and neutropenia, respectively. There were no cases of delayed chemotherapy. With a median follow-up of 64.5 months, 3 patients died after recurrence of metastases. *Conclusion*: cisplatin - paclitaxel combined with postoperative radiotherapy has been shown to be highly effective and safe in Chinese women with localised uterine cervical cancer. The dose-limiting toxicities are 35 mg/m^2 cisplatin and 30 mg/m^2 paclitaxel per week for at least 6 cycles.

Keywords

Localised Uterine Cervical Cancer, Weekly Cisplatin-Paclitaxel, Concomitant Chemoradiotherapy

1. Introduction

Uterine cervical cancer (UCC) remains a major cause of cancer morbidity and mortality worldwide (1). Every year, approximately 65,000 new cases and over 25,000 deaths are attributed to UCC in China [1]. The curative treatment of this

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Received: 15 August 2025; **Accepted:** 26 August 2025; **Published:** 23 September 2025

disease is fraught with challenges, 10-25% of women with early-stage UCC recur after radical hysterectomy alone [2]. The 5-year survival rate for patients at high risk of recurrence varies between 40% and 58%. This survival rate falls to less than 10% after recurrence [3]. Compared to surgery alone, postoperative radiotherapy (PORT) in patients with high risk of recurrence significantly reduces the failure rate after treatment [3-5]. Several authors have reported that PORT combined with weekly cisplatin-based chemotherapy improved survival in high-risk patients compared with radiotherapy (RT) alone [5, 6]. Therefore, concomitant cisplatin-based chemoradiotherapy has become the standard in the postoperative treatment for early-stage UCC with a high risk of recurrence [6]. However, in order to improve clinical outcomes, different chemotherapy combination regimens have been explored in some centers [7]. Paclitaxel used as a radiosensitising agent in recurrent UCC has demonstrated the superiority of the combination with cisplatin over cisplatin alone [7-11]. Despite these results, many physicians remain reluctant to apply the cisplatin-paclitaxel protocol as a standard of weekly chemotherapy regimen concomitant with PORT [12, 13]. Furthermore, due to the disparity in treatment tolerance between the Chinese population and that of Sub-Saharan African, Caribbean, and Western countries, we initiated a study of cisplatin-paclitaxel in a weekly regimen concomitant with PORT. The objective was to determine the maximum tolerated dose and dose-limiting toxicity of concomitant chemotherapy in 30 Chinese women undergoing surgery for localized UCC.

2. Materials and Methods

2.1. Eligibility Criteria

We prospectively analysed data from patients who underwent UCC surgery and received weekly chemotherapy concomitant with adjuvant RT in the 4th Affiliated Hospital of Hebei Medical University from January 2017 to May 2020. The present study was approved by the Ethics Committee of the 4th Affiliated Hospital of Hebei Medical University and all patients signed an informed consent form prior to inclusion. Patient were eligible according to the following criteria: (1) Histological confirmation of medium-risk UCC (age ≤35 years, lymphovascular invasion, invasion of more than 1/3 of the stroma in depth, tumour size ≥ 4 cm, rare histology) or high-risk (positive resection margins, lymph node involvement and/or parametrial involvement) of recurrence; (2) FIGO clinical stage I - IIB and cT1- T2b, N0 M0, according to the International Union Against Cancer classification (UICC, 2017); (3) A KPS index ≥70%; (4) Absence of renal impairment (creatinine clearance ≥ 60 ml/min according to Cockcroft); (5) No anticancer treatment prior to inclusion; (6) Having received regular follow-up ≥ 6 months. They were excluded if any of the following non-inclusion criteria were met: (1) Clinical stage ≥ stage III; (2) Previous chemotherapy and/or radiotherapy; (3) Presence of renal insufficiency (creatinine clearance < 60 ml/min according to Cockcroft) that would make chemotherapy intolerable.

2.2. Exclusion Criteria

They were excluded in the presence of one of the contra-indications to irradiation: fistula or pregnancy.

2.3. Treatment Regimens

2.3.1. Radiotherapy

(i). Simulation CT Scan and Target Volume Definition

All patients included in the present study underwent a simulation CT scan (3 mm slice) in the supine position and under a thermoformed thoraco-abdominal mask. The positioning protocol was performed with a full bladder. One hour before the scan, patients were systematically asked to drink between 300 and 500 ml of mineral water. In the absence of contraindications, the scans were invariably injected and the images were then transmitted digitally via the internet and reconstructed in three dimensions (3D) in the treatment planning system. Post- operative external beam radiotherapy (EBRT) was followed by brachytherapy. Pelvic irradiation was administered by intensity-modulated radiotherapy (IMRT) or image-guided radiotherapy (IGRT). The clinical target volume (CTV) included the vagina cuff to 3 cm lower, the lymphatic drainage tracts: internal iliac, external iliac, common iliac, obturator, presacral and para-aortic. The upper limit of the CTV corresponded to half of the 4th lumbar vertebra, and the lower limit to the lower edge of the obturator foramen. The predicted target volume (PTV) was defined as an expansion of 5-10 mm around the CTV [14].

(ii). Radiotherapy Planning, Doses and Dose Constraints

The total dose of EBRT prescribed for the PTV was 45 - 60 Gy/25 - 30fractions of 1.8-2Gy per fraction. Dose-volume constraints were defined for the small bowel (V30 < 40%, Dmax < 52 Gy), bladder (V45 < 45%) and rectum (V45 < 60%), which were adjacent to the CTV. For endocavitary brachytherapy, high dose rate irradiation was administered using 192 Ir, 5 Gy/fractions, 2 times/week, with a total of 2 to 4 sessions. The total duration of EBRT and brachytherapy was ≤ 7 weeks [14].

2.3.2. Chemotherapy and Dose Escalation

Referring to the standard protocol of 6 cycles of weekly cisplatin- and cisplatin-paclitaxel-based chemotherapy in national and international clinical trials [10, 14-16], the initial dose of weekly chemotherapy molecules in this study was 20 mg/m^2 cisplatin and 10 mg/m^2 paclitaxel. Using a 5 + 5 design,

a total of 6 dose level groups were established, with the first 5 patients escalated until the dose-limiting toxicity level was reached. According to the Common Terminology Criteria for Adverse Events (CTCAE) 4.0 criteria [17], the following acute toxicities were considered serious adverse events: grade 3 and 4 haematological toxicities and grade 3 or 4 non-haematological toxicities, which do not include alopecia, nausea and vomiting, loss of appetite and weakness or lipothymia. During the procedure, if no serious adverse events occurred in a particular dose group, we escalate the dose to the next group. However, if 1 of the 5 cases develops a serious adverse event, we add 5 new cases in the same dose level group. If in the newly formed group a serious adverse event recurs, we define this dose level group as the dose-limiting toxicity level. If 3 out of 5 patients in a given dose level group develop a serious adverse event, we also define this group as the dose-limiting toxicity level. The dose level before dose-limiting toxicity is called the maximum tolerated dose. If no serious adverse events recur, we move on to the next dose level group. If dose-limiting toxicity does not occur throughout the trial, the last dose level group is defined as the maximum tolerated dose level.

2.3.3. Chemotherapy and Dose Modification

Chemotherapy started on the first day of RT, with one course per week for 6 cycles. Paclitaxel was dissolved in 250 ml of 0.9% NaCl and administered intravenously over 1 hour. Cisplatin is then introduced intravenously, initially at 20 mg/m^2 and then progressively, without exceeding 70 mg/m^2, in 500 ml of 0.9% NaCl. To prevent chemotherapy-induced allergic reactions and vomiting, an injection of corticosteroid and ondansetron 8 mg was given intravenously 15 minutes before each course of chemotherapy. Systematic weekly monitoring was carried out to assess the patients' biological parameters and general condition, as well as the acute effects of chemoradiotherapy. Supportive symptomatic treatment was administered depending on the adverse event.

2.4. Post-Therapy Evaluation and Follow-up

Acute adverse events were evaluated according to CTCAE 4.0 criteria and late reactions according to Radiation Therapy Oncology Group (RTOG) criteria [17].

2.5. Statistical Analyses

Patient data were collected consecutively and extracted from the electronic database of the 4th Affiliated Hospital of Hebei Medical University. The information obtained was entered and analysed using SPSS version 24.0 software (SPSS Inc., Chicago, IL). Survival was determined using the Kaplan Meier method.

3. Results

Patients anatomo-clinical baselines characteristics

From January 2017 to May 2020, data from 78 patients operated on for UCC were extracted from the electronic database. Of these, 30 patients were included in the study, 46 patients were not included and 02 patients were excluded from the study (Figure 1). The median age was 57 years (32-78 years). The baseline clinical characteristics of all patients are shown in Table 1. The cancer was classified as stage I A in 3 cases, stage I B1 in 4 cases, stage I B2 in 4 cases, stage IIA in 13 cases and stage II B in 6 cases. The histological type was dominated by squamous cell carcinoma 21 cases, adenocarcinoma 6 cases, sarcoma 1 case, lymphoma 1 case and clear cell carcinoma 1 case. It was well differentiated in 16 cases (53.3%), moderately differentiated in 5 cases (16.7%) and undifferentiated in 9 cases (30.0%).

Acute toxicities

Acute haematological toxicities in the 6 groups were mainly dominated by leucopenia and neutropenia. They were frequent after the 4th and 6th weeks of chemotherapy and are detailed in Table 2. In the first 4 groups, 5 patients and 1 patient in the dose level 6 experienced grade 3 and 4 leukopenia, respectively. Chemotherapy was achieved after leukocyte levels had normalised. At week 4, 1 patient in dose level 6 developed grade 4 leukopenia and neutropenia. These serious adverse events required administration of recombinant human granulocyte colony stimulating factor to normalise leukocyte and neutrophil counts, and completion of the 6th cycle of chemotherapy after a 20% dose reduction of both chemotherapeutic agents. No allergic, infectious, renal, auditory or neurological toxicities were observed in group 6. Gastrointestinal toxicities were all nausea, diarrhoea or urgency grade $\leq$ 2. Some patients developed grade 1 and 2 anaemia, skin reactions, urinary tract symptoms and fatigue. All these symptoms were tolerated after symptomatic treatment and supportive oncology care. In the dose level 5 group, with 40 mg/m^2 cisplatin and paclitaxel, we observed grade 3 leukopenia and neutropenia in 3 patients. The patients were treated with supportive oncology care and returned to normal. Dose-limiting toxicity was reached in 2 of the patients with a severe adverse event of grade 3 diarrhoea after 4 weeks, which necessitated discontinuation of treatment.

Twenty-seven out of 30 patients completed the 6 cycles of chemotherapy as planned. One of 5 patients in dose level 1 developed grade 2 diarrhea 3 weeks after chemotherapy and was unable to continue chemotherapy. Of the 3 patients in dose group 3, 1 developed a urinary tract infection and fever at 5 weeks after removal of the ureteral catheter. One of the 4 patients in group 6 was treated for grade 1 thrombocytopenia after 5 weeks of chemotherapy. The patient refused further chemotherapy due to adverse events. All patients completed external and intracavity irradiation within 7 weeks. There were no delays in the duration of treatment due to concomitant chemotherapy.

Metastatic progression and survival

The end-point of follow-up was fixed to 31/12/2022. Median follow-up was 64.5 months (23.5 to 78 months). Three patients died after developing local recurrence and distant metastases, giving a 90.0% survival rate. One patient with a moderately differentiated mucinous adenocarcinoma had a vaginal stump recurrence with bladder infiltration at 8.4 months and died at 37.9 months after resumption of palliative chemotherapy. One patient with low-grade sarcoma presented at 10 months with intra pelvic recurrence and inguinal lymph node metastases, initially treated with chemoradiotherapy, underwent endoscopic resection for a bladder tumor at 12 months and died at 17.3 months before the start of palliative chemotherapy. A patient with squamous cell carcinoma developed multiple lymph node metastases in the retroperitoneum and left supraclavicular region after 30 months and died at 33 months.

Late toxicities

One patient in dose level 5 with a ureteral catheter inserted during surgery developed a urinary tract infection during PORT and 60 months after developed a double ureteral stenosis with a recurrent urinary tract infection. In one patient, we observed non-disabling edema of the left lower limb with numbness after PORT.

4. Discussion

UCC is one of the most common gynecological malignancies worldwide, and advanced disease is associated with a poor prognosis [1]. Surgery and RT are two distinct treatment methods associated with similar disease-free survival and overall survival rates in women with early-stage disease [4-6]. However, although most women benefit from surgery in the first instance, many are prescribed adjuvant RT because of the presence of certain pejorative factors identified on pathological examination of the hysterectomy specimen [5]. Several authors have reported that concomitant chemoradiotherapy is more effective in the postoperative treatment of UCC at high risk of recurrence, due to a better survival rate demonstrated in prospective studies [6, 7]. On the other hand, for patients at intermediate or middle risk of recurrence, some studies have suggested that patients with infiltration of more than half of the myometrium have a better outcome after adjuvant chemotherapy [15, 16, 18]. However, in the absence of evidence-based data, there is no consensus on the best adjuvant treatment option for patients at intermediate risk. Our study involved patients operated on for early-stage UCC, with intermediate risk factors or at high risk of recurrence. The aim was to determine the maximum tolerated dose of weekly chemotherapy concomitant with PORT. In clinical practice, cisplatin 40 mg/m^2 is the most commonly used weekly chemotherapy regimen with RT in the treatment of UCC [19]. While Geara FB et al [20] have confirmed for a decade that paclitaxel alone was an effective radiosensitiser, its combination with cisplatin in early-stage UCC was well tolerated and clinically effective in increments of 10mg/m^2 to 50mg/m^2 per week every 3 weeks [20]. Similarly, Boardman CH et al [11] also reported that the maximum tolerated dose of weekly chemotherapy was 135mg/m^2 for paclitaxel and 50mg/m^2 for cisplatin, with a total of 6 cycles. Based on these results reported in the literature, our study used the weekly chemotherapy regimen of the Gynecologic Oncology Group [21] to define the maximum dose tolerated by Chinese women.

At the end of the analysis, the maximum tolerated dose of the two anti-cancer agents in a concomitant chemoradiotherapy protocol of 6 weekly cycles was 35 mg/m^2 of paclitaxel and 30 mg/m^2 of cisplatin; dose-limiting toxicities were dominated by grade 3 diarrhoea. Umayahara K et al [22] found a higher maximum tolerated dose of paclitaxel, 50 mg/m^2 weekly in Japan. However, the dose-limiting toxicities were almost similar to those observed in our study. In addition, the occurrence of gastrointestinal toxicities, including diarrhoea, is a serious problem during concomitant chemoradiotherapy, often resulting in delayed or omitted chemotherapy treatments and even having an impact on prognosis. In our study, it should be noted that the regimen was an adjuvant treatment. Therefore, patient tolerance is likely to be different from that in the Umayahara K et al study, and intestinal reactions such as diarrhoea, vomiting or nausea may be more likely to occur. The administration of antidiarrhoeal agents such as loperamide hydrochloride and antiemetics such as ondansetron and metoclopramide were effective in controlling acute gastrointestinal reactions. With regard to haematological toxicities, neutrophil leukopenia in particular is one of the main dose-limiting factors for cisplatin and paclitaxel [23]. In our series, haematological adverse events were dominated by grade 1 and 2 toxicities, and generally occurred between the 4th and 6th week of the last cycle of chemotherapy. Beyond grade 1 or 2 toxicities, we observed one case of grade 4 leukopenia in the dose level 6 group. The high incidence of grade 3 and 4 leukopenia in the weekly chemotherapy regimen concomitant with radiotherapy is to be expected and has been reported previously [23]. However, it was low with our protocol of weekly cisplatin-paclitaxel-based chemotherapy concomitant with PORT. However, the administration of human granulocyte colony growth factors and recombinant human interleukin-11 can fundamentally restore the situation without affecting the duration of treatment. In our case, we administered 2 doses of human granulocyte colony growth factor and the patient recovered to normal health 3 days after emergency hospitalisation with supportive oncology care. No acute events significantly delayed treatment, and the rapidity and administration of adequate supportive care enabled the patient to continue the normal course of treatment. These observations corroborate the data in the literature [16]. Furthermore, with regard to late complications, only one patient in the dose level 5 group developed a urinary tract infection during PORT due to the presence of a double J catheter placed during surgery. Six months after RT, ureteral stenosis developed. The present study now shows that urinary

tract infections are associated with the presence of urethral catheters, and that urinary symptoms disappear progressively at the end of RT and after removal of the catheters. The results obtained suggest that the late complications occurring at the end of the chemotherapy treatment, 35 mg/m^2 of paclitaxel and 30 mg/m^2 of cisplatin for 6 weekly cycles, are acceptable, but its capacity to induce an effective synergy in association with RT on local control and long-term survival deserves to be studied in depth.

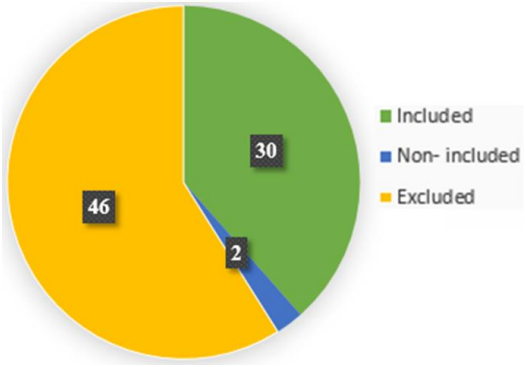

Figure 1. *Distribution of cases according to inclusion, non-inclusion and exclusion criteria.*

Table 1. *Patients anatomo clinical baselines characteristics (n=30).*

Characteristics	Cases	Percentage (%)
Median age (years)	57 ± 2.3	
35 - 55	21	70.0
> 55	09	30.0
KPS		
≥ 70	30	100
< 70	0	-
High (cm)		
≥ 4	22	73.3
< 4	08	26.7
Clinical stage (FIGO, 2017)		
I	11	36.7
IIA	13	43.3
IIB	06	20.0
Histology		
Squamous cell carcinoma	21	70.0
Non-squamous	09	30.0
Degree of infiltration		
≥ ½	23	76.7
< ½	07	23.3
Lymphovascular infiltration		
Yes	13	43.3
No	17	56.7
Parametrium infiltration		
Yes	18	60.0
No	12	40.0
Differentiation grade		
Well differentiated	16	53.3
Moderately differentiated	05	16.7
Undifferentiated	09	30.0
Status of resection margins		
Positive	09	30.0
Negative	21	70.0
Radiotherapy technique		
IMRT	18	60.0
IGRT	12	40.0

KPS: Karnofsky performance status; *IMRT:* Intensity modulated radiotherapy; *IGRT*: Image guided radiotherapy.

Table 2. *Common acute toxicities of weekly paclitaxel - cisplatin in early-stage cervical cancer (n=30).*

Acute toxicities	Group 1 15 Weeks	Group 2 18 Weeks	Group 3 25 Weeks	Group 4 20 Weeks	Group 5 32 Weeks	Group 6 30 Weeks
Heamatology						
Heamoglobin (g/dl)						

Acute toxicities	Group 1 15 Weeks	Group 2 18 Weeks	Group 3 25 Weeks	Group 4 20 Weeks	Group 5 32 Weeks	Group 6 30 Weeks
≤ 8	0	1	2	0	2	0
> 8	15	16	25	20	30	30
Leukopenia (Grades)						
0	6	13	16	10	18	18
1	4	3	5	4	5	8
2	5	1	3	3	4	2
3	0	1	1	2	3	1
4	0	0	0	1	0	1
Neutropenia (Grades)						
0	6	14	17	10	16	16
1	4	3	5	4	7	8
2	5	1	3	5	5	3
3	0	0	0	0	3	2
4	0	0	0	1	0	1
Thrombopenia (Grades)						
0	6	13	16	10	18	23
1	4	3	5	4	7	1
2	5	1	3	4	5	3
3	0	1	1	1	2	2
4	0	0	0	1	0	1
Gastro-intestinal	6	13	16	10	18	17
Diarrheoa (Grades)						
0	7	13	16	10	18	17
1	4	4	6	4	7	8
2	5	1	3	6	5	3
3	0	0	0	0	2	2
4	0	0	0	0	0	0
Nausea/vomiting (Grades)						
0	10	13	16	10	18	17
1	4	3	5	4	7	8
2	1	1	3	4	5	3
3	0	1	1	1	2	2
4	0	0	0	1	0	0

7. Conclusion

Weekly cisplatin-paclitaxel chemotherapy concomitant with PORT proved effective and well tolerated. The maximum tolerated dose in Chinese women is 30 mg/m^2 cisplatin and 35 mg/m^2 paclitaxel weekly for 6 weeks. Prospective studies with a larger sample size and a longer follow-up period are needed to validate these results.

Abbreviations

EBRT	External Beam Radiotherapy
IGRT	Image Guided Radiotherapy
IMRT	Intensity Modulated Radiotherapy
KPS	Karnofsky Performance Status
PORT	Postoperative Radiotherapy
RT	Radiotherapy
UCC	Uterine Cervical Cancer

Acknowledgments

We would like to thank Dr Chen XI for help with an earlier version of the manuscript and Pr. Hong Liu for her critical reading of an earlier version of the manuscript.

Author Contributions

Mamady Keita: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Supervision, Validation, Writing - original draft, Writing - review & editing

Chen Xi: Data curation, Investigation

Abou Camara: Formal Analysis, Methodology, Software

Arbaba Balde: Formal Analysis, Methodology, Writing - review & editing

Kalil Cisse: Formal Analysis, Methodology, Writing - review & editing

Funding

The authors would like to thank the Natural Science Foundation of Hebei Province (No. H2021206429).

Conflicts of Interest

The authors declare no conflicts of interest.

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