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ORIGINAL ARTICLE

Clinical analysis of uterine arterial interventional chemoembolization combined with radiotherapy in mid-advanced cervical cancer

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Summary

Purpose: *The purpose of this study was to compare the efficacy and safety of uterine arterial interventional chemoembolization (UAIC) combined with radiotherapy and intravenous chemotherapy combined with radiotherapy in the treatment of mid-advanced cervical cancer.*

Methods: *A total of 128 patients with mid-advanced cervical cancer were divided into UAIC group (n=64; Docetaxel + nedaplatin UAIC combined with intensity-modulated radiotherapy) or Control group (n=64; docetaxel + nedaplatin intravenous chemotherapy combined with intensity-modulated radiotherapy). The tumor recurrence and survival status were recorded during follow-up, and the progression-free survival (PFS) and overall survival (OS) were compared between the two groups.*

Results: *The short-term clinical response rate was 70.3% and 48.4%, respectively, in UAIC group and control group. The scores of physical function, role function, cognitive function, emotional function and social function were higher in UAIC group than those in control group, but only the emotional function score had a statistically significant difference. In the symptom scales, the scores of sleep disturbance, nausea and vomiting, pain and fatigue were obviously lower in UAIC group than those in control group. The follow-up results revealed that the 3-year OS was 70.3% and 73.4%, and the 3-year PFS was 64.1% and 65.6%, respectively, in UAIC group and control group. Moreover, it was found through log-rank test that OS and PFS had no statistically significant differences between the two groups.*

Conclusions: *UAIC combined with radiotherapy has better short-term clinical efficacy than intravenous chemotherapy combined with radiotherapy in the treatment of mid-advanced cervical cancer, with fewer adverse reactions and higher quality of life, but it has no significant effect on the long-term survival and tumor progression in patients.*

Key words: *cervical cancer, radiotherapy, interventional chemoembolization, intravenous chemotherapy, efficacy*

Introduction

Cervical cancer is a clinically common malignant tumor, and its incidence has been rising year by year and shown a younger tend. Clinically, patients with mid-advanced cervical cancer are mostly treated with radiotherapy combined with chemotherapy [1]. However, they have complicated conditions often accompanied by metastasis, so routine concurrent radiochemotherapy combined with intravenous chemotherapy has less excellent efficacy and a weaker effect on controlling tumor diameter [2,3]. Recent studies have shown that pre-radiotherapy induction chemotherapy and concurrent radiochemotherapy can effectively control the clinical symptoms and prolong the survival time of patients with mid-advanced cervical cancer, but their effects are greatly affected by chemotherapy complications and chemotherapy drugs [4-6].

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Arterial interventional chemoembolization can directly infuse chemotherapy drugs into the lesions through regional arteries, thereby killing tumor cells. Concurrent radiochemotherapy can achieve better effects [7,8]. The present study aims to compare the efficacy and safety of uterine arterial interventional chemoembolization (UAIC) combined with intensity-modulated radiotherapy and intravenous chemotherapy combined with intensity-modulated radiotherapy in the treatment of mid-advanced cervical cancer, so as to provide references for the selection of therapeutic regimen for such patients.

Methods

General data

The clinical data of 128 patients with mid-advanced cervical cancer were retrospectively analyzed. All patients were aged 27-67 years old, with a median of 50.59 years old. They all underwent pathological examination, gynecological examination, hematology examination, tumor marker examination and related imaging examinations before radiochemotherapy. Inclusion criteria: 1) patients diagnosed with malignant cervical tumor in clinical stage IIb-IIIb *via* cervical biopsy, 2) those with a Karnofsky performance scale score ≥70 points, and 3) those without extrapelvic metastasis confirmed by enhanced computerized tomography (CT) or magnetic resonance imaging (MRI). Exclusion criteria: 1) patients with a history of chemotherapy, radiotherapy or other treatments, 2) those with severe mental disorders or dysfunction in the heart, liver or kidney, 3) those with severe coagulation dysfunction or anemia, or 4) those complicated with other malignant tumors. The patients were divided into two groups according to different treatment methods. Docetaxel + nedaplatin UAIC combined with intensity-modulated radiotherapy was performed in UAIC group (n=64), while docetaxel + nedaplatin intravenous chemotherapy combined with intensity-modulated radiotherapy was performed in control group (n=64). As shown in Table 1, the baseline data such as age, gender, tumor pathological type and stage had no statistically significant differences between the two groups (p>0.05). All patients selected were informed of the study according to the *Declaration of Helsinki* and signed the informed consent. This study was approved by the Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region.

Treatment methods

Docetaxel + nedaplatin intravenous chemotherapy combined with intensity-modulated radiotherapy was performed in control group. In the first cycle of chemo-

Table 1. Baseline demographic and clinical characteristics of the studied patients

Characteristics	*UAIC group (n=64)* *n (%)*	*Control group (n=64)* *n (%)*	*p value*
Age, years	49.74±10.03	51.14±9.97	0.430
Histology			0.449
Squamous cell carcinoma	48 (75.0)	43 (67.2)	
Adenocarcinoma	13 (20.3)	19 (29.7)	
Adenosquamous carcinoma	3 (4.7)	2 (3.1)	
Tumor size (cm)	4.18±0.47	4.25±0.51	0.321
FIGO stage			0.479
II B	7 (10.9)	11 (18.2)	
III A	43 (67.2)	37 (57.8)	
III B	14 (21.9)	16 (25.0)	
Differentiation grade			0.644
High	18 (28.1)	16 (25.0)	
Middle	28 (43.8)	26 (40.6)	
Low	18 (28.1)	22 (34.4)	
Type of tumor growth			0.506
Cauliflower type	25 (39.1)	27 (42.2)	
Infiltrating type	17 (26.6)	13 (20.3)	
Endophytic type	22 (34.4)	24 (37.5)	

UAIC: uterine arterial interventional chemoembolization; FIGO: Federation of Gynecology and Obstetrics.

therapy, docetaxel was injected intravenously at 75 mg/m^2 for 3 h in the dark at 1 d, and nedaplatin was injected intravenously at 80 mg/m^2 at 2 d. During chemotherapy, patients were given routine symptomatic treatments such as anti-allergy and anti-vomiting. The second cycle of chemotherapy was performed after 3 weeks. A Philips large-aperture CT simulator was used for radiotherapy positioning. The patient was fixed with a vacuum pad in a supine position with his hands holding his head. Before positioning, the patient was required to fill the bladder appropriately and empty the rectum. During positioning, CT scan was performed from the inferior margin of the first lumbar vertebra to 5 cm below the ischial tuberosity, and the scan thickness was about 5 mm. The clinical target volume (CTV) was delineated, covering the uterine body, parauterine tissue, cervix, part of the vagina and lymphatic drainage region. Next, CTV was expanded outward by 1.0 cm in the cephalo-caudal direction, 0.7 cm in the left-right direction, and 0.8 cm in the abdomen-back direction, forming the planning target volume (PTV). The treatment plan was developed using Oncentra or Monaco planning system: 7-field irradiation was conducted at a prescribed dose of 50.4 Gy once a day (1.8 Gy per time, 5 times per week) for 28 d, 28 times in total. Organ-at-risk volume (V) is as follows: rectum V50 <50%, bladder V50 <50%, left-right femoral heads V50 <5%, small intestine V50 <10%, bilateral kidneys V20 <20%, spinal cord V_{max} <40 Gy. The plan was assessed: >95% of PTV was covered by the prescribed dose, and there was no cold point within the CTV; <10% of PTV was covered by 110% of the prescribed dose, and <2% of PTV was covered by 115% of the prescribed dose; there was no hot point on the anterior wall of the rectum and the posterior wall of the bladder. After the plan was accepted, a Varian Acuity simulator was used for position verification, and the error needed to be strictly controlled within 5 mm. If the error was >5 mm, re-adjustment was needed. Finally, cone beam CT (CBCT) was used for three-dimensional position verification once a week during treatment.

Docetaxel + nedaplatin UAIC combined with intensity-modulated radiotherapy was performed in UAIC group. The femoral artery was punctured using Seldinger's technique. Under the monitoring with digital subtraction angiography (DSA), a 5F Cobra tube was inserted into the uterine artery, and the angiography was performed to determine the blood supply of tumor. The mixed solution of gelatin sponge particles and 1/3 dose of the above-mentioned chemotherapy drugs was used to embolize bilateral uterine arteries until the uterine staining disappeared, and the bilateral main uterine arteries were retained. 560-710 μm gelatin sponge particles were used as the embolic agent. The course of treatment, symptomatic treatment and radiotherapy were the same as those in control group.

Observation indexes

Short-term clinical efficacy was assessed after treatment based on the shrinkage of the tumor and the presence or absence of new lesions. According to the Response Evaluation Criteria In Solid Tumors, complete response (CR): the tumor completely disappears for more than 4 weeks without new lesions. Partial response (PR): the tumor volume shrinks by ≥50% and there are no new lesions. Stable disease (SD): the tumor volume shrinks or expands by <50% and there are no new lesions. Progressive disease (PD): the tumor volume expands by ≥25%, or there are new lesions. Response rate = (CR + PR)/total cases × 100%. During treatment, the incidence of adverse reactions was recorded and compared between the two groups.

The quality of life of all patients was surveyed using the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30), and those who had communication and understanding disorders and refused the survey were excluded. EORTC-QLQ-C30 covers 5 functional scales, 3 symptom scales, 1 global quality of life scale and 6 single symptom items. The higher the scores of global quality of life scale and functional scales, the higher the quality of life. On the contrary, the higher the scores of symptom scales and single items, the lower the quality of life [9].

The patients were reexamined in outpatient clinics every 1-2 months within the first year after treatment, every 3 months in the second year, and every 3-6 months in the third year. The general examination, pelvic examination, cervical cytology examination, pelvic B-mode ultrasound, and chest X-ray were performed, as well as CT or MRI if necessary. The survival status and progression-free survival (PFS) of patients were recorded, and the patients were followed up until May 2020.

Statistics

22.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. Measurement data were expressed as mean ± standard deviation (x±s), and t-test was performed for intergroup comparison. Enumeration data were expressed as rate (%), and x^2 test was performed for intergroup comparison. The survival curves were plotted using the Kaplan-Meier method, and whether there is a statistically significant difference in the survival rate between the two groups was detected using log-rank test. $p<0.05$ suggested the statistically significant difference.

Results

Comparison of short-term clinical efficacy between the two groups

The short-term clinical efficacy was evaluated in all patients after treatment. In UAIC group, there were 12 cases (18.8%) of CR, 33 cases (51.6%) of PR, 15 cases (23.4%) of SD, and 4 cases (6.3%) of PD, with a response rate of 70.3% (45/64). In control group, there were 8 cases (12.5%) of CR, 23 cases (35.9%) of PR, 26 cases (40.6%) of SD, and 7 cases (10.9) of PD, with a response rate of 48.4% (31/64). It could be observed that short-term clinical response rate had a statistically significant difference

between the two groups, which was significantly better in UAIC group than that in control group (p=0.012) (Table 2).

Comparison of treatment-related adverse reactions between the two groups

Treatment-related adverse reactions in the two groups mainly included myelosuppression, gastrointestinal reactions, liver-kidney function damage, alopecia or neurotoxicity, fever or pelvic pain, radiation dermatitis, radiation cystitis and radiation proctitis, which were all in grade I-II and all improved after symptomatic treatment. In UAIC group and control group, the incidence rate of myelosuppression was 18.8% and 51.6%, that of gastrointestinal reactions was 25.0% and 46.9%, that of liver-kidney damage was 4.7% and 29.7%, and that of alopecia or neurotoxicity was 9.4% and 40.6%, respectively. The above incidence rates were obviously lower in UAIC group than those in control group (p<0.05). Meanwhile, the incidence rate of fever or pelvic pain was 23.4% and 7.8%, respectively, which was obviously lower in UAIC group than that in control group (p=0.015). There was no statistically significant difference in the incidence of other adverse reactions (p>0.05) (Table 3).

Comparison of EORTC-QLQ-C30 scores between the two groups

In the functional scales of EORTC-QLQ-C30, the scores of physical function, role function, cognitive function, emotional function and social function were higher in UAIC group than those in control group, but only the emotional function score had a statistically significant difference [(78.73±10.38) points *vs.* (74.96±10.13) points, p=0.040], and other scores had no statistically significant differences (p>0.05). In the symptom scales, the scores of sleep disturbance, nausea and vomiting, pain and fatigue were obviously lower in UAIC group than those in control group (p<0.05), while other symptom scores had no statistically significant differences (p>0.05). The general health score was (79.46±11.28) points and (78.17±13.49) points, respectively, in UAIC group and control group, showing no statistically significant difference (p=0.358) (Table 4).

Table 2. Clinical effective rates of the two studied groups

	UAIC group n=64 *n (%)*	*Control group n=64* *n (%)*	*p value*
CR	12 (18.8)	8 (12.5)	
PR	33 (51.6)	23 (35.9)	
SD	15 (23.4)	26 (40.6)	
PD	4 (6.3)	7 (10.9)	
RR	45 (70.3)	31 (48.4)	0.012

UAIC: uterine arterial interventional chemoembolization; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; RR: response rate.

Table 3. Comparison of adverse reactions of the studied patients in two groups

	UAIC group (n=64) *n (%)*	*Control group (n=64)* *n (%)*	*p value*
Myelosuppression	12 (18.8)	33 (51.6)	0.001
Gastrointestinal reactions	16 (25.0)	30 (46.9)	0.010
Liver/Renal function damage	3 (4.7)	19 (29.7)	0.001
Alopecia & Neurotoxicity	6 (9.4)	26 (40.6)	0.001
Fever & Pelvic pain	15 (23.4)	5 (7.8)	0.015
Radiation dermatitis	5 (7.8)	4 (6.3)	0.730
Radiation cystitis	8 (12.5)	10 (15.6)	0.611
Radiation proctitis	6 (9.4)	7 (10.9)	0.698

Uterine arterial interventional chemoembolization.

Follow-up results of patients' survival status

All patients were followed up for 7-36 months until May 2020, with a median of 30.1 months. In UAIC group and control group, the 1-, 2- and 3-year OS was 96.9% (62/64) and 95.3% (61/64), 82.8% (53/64) and 87.5% (56/64), and 70.3% (45/64) and 73.4% (47/64), respectively. The 1-, 2- and 3-year PFS was 87.5% (56/64) and 90.6% (58/64), 75.0% (48/64) and 76.6% (49/64), and 64.1% (41/64) and 65.6% (42/64), respectively. The Kaplan-Meier survival curves of patients are shown in Figure 1. It was found through log-rank test that OS and PFS had no statistically significant differences between the two groups (p=0.618, p=0.785).

Discussion

Surgery is the preferred treatment for early cervical cancer, but the opportunity of surgery has been lost for advanced cervical cancer, so comprehensive treatment covering a variety of treatment methods should be adopted, including interventional chemoembolization, neoadjuvant intravenous chemotherapy, and intensity-modulated radiotherapy [10]. It is believed by most scholars that pre-radiotherapy local or systemic chemotherapy can exert a synergistic effect with radiotherapy to significantly improve the efficacy on patients with advanced cervical cancer, and it

Table 4. Comparison of posttreatment EORTC-QLQ-C30 scale scores (points) between the two groups of patients

	UAIC group (n=64)	*Control group (n=64)*	*p value*
Functioning scales			
Physical	78.56±12.59	76.78±10.41	0.385
Role	80.42±9.34	79.10±9.19	0.422
Emotional	78.73±10.38	74.96±10.13	0.040
Social	76.71±11.31	75.44±11.64	0.532
Cognitive	84.36±10.57	82.69±11.18	0.387
Symptom scales			
Appetite loss	24.52±13.47	26.94±12.87	0.041
Constipation	26.83±12.93	27.71±13.35	0.505
Dyspnea	25.11±14.26	27.89±12.68	0.246
Financial impact	42.14±14.82	41.24±13.51	0.620
Sleep disturbance	22.83±14.63	25.05±14.45	0.049
Nausea and vomiting	49.67±11.37	53.17±12.59	0.038
Pain	46.88±12.94	51.31±14.61	0.039
Fatigue	64.58±11.75	68.84±10.60	0.033
General health condition	79.46±11.28	78.17±13.49	0.358

UAIC: uterine arterial interventional chemoembolization; EORTC: European Organization for Research and Treatment of Cancer.

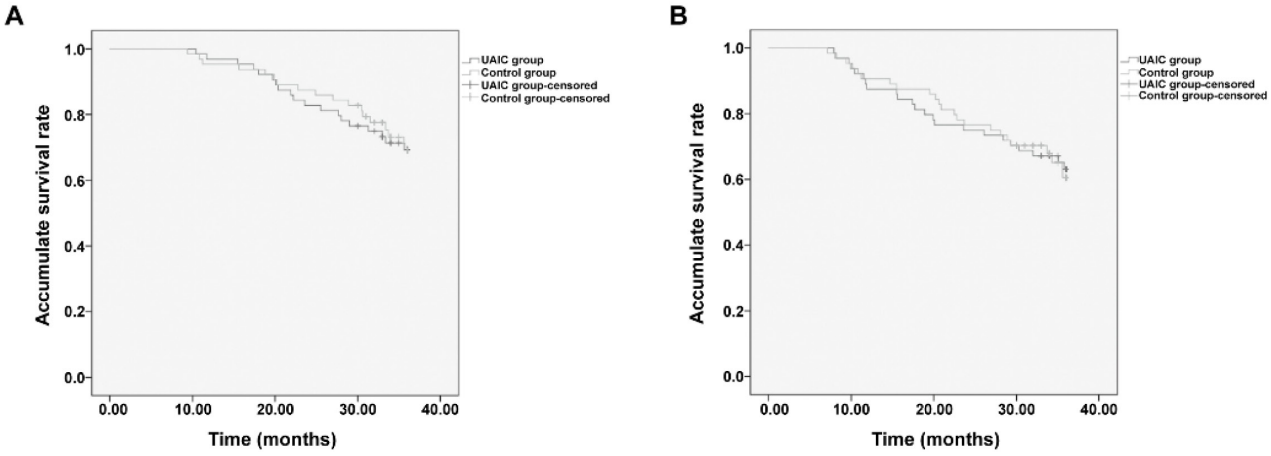

Figure 1. Kaplan-Meier survival curve of patients in the two groups. The differences in the overall survival rate **(A)** and progression free survival rate **(B)** of patients between UAIC group and control group had no statistical significance. (p=0.618, p=0.785).

can also effectively lower the clinical stage of cervical cancer, winning the opportunity for surgical treatment [11,12]. Conventional radiotherapy and intravenous chemotherapy have definite curative effects, but there is a contradiction between the good curative effect and the unsatisfactory prognosis of patients, and the quality of life of patients is also not ideal [13]. However, tumor cells can be killed through directly injecting nedaplatin into the uterine artery *via* interventional means to raise the local drug concentration, and reducing or blocking the blood supply of tumor to lead to hypoxic ischemic necrosis of lesions. At the same time, the first-pass effect of drug metabolized by the liver and kidneys is prevented, and the risk of drug failure due to binding to plasma proteins is reduced [14,15].

Nedaplatin is a first-line anti-tumor drug widely used in China. As a second-generation platinum drug, it is characterized by a broad anti-tumor spectrum, a wide range of combined chemotherapy, a synergistic effect combined with radiotherapy, no cross-resistance with cisplatin, and fewer adverse reactions [16]. Currently, platinum-based concurrent radiochemotherapy is the standard treatment for mid-advanced cervical cancer [17]. Chemotherapy drugs kill tumor cells through destroying tumor cells and their self-repair ability, and realizing the synchronization between damaged cell cycle and radiosensitivity cycle [18].

In the present study, both interventional chemoembolization and intravenous chemotherapy combined with intensity-modulated radiotherapy had a higher clinical response rate, but it was far higher in UAIC group than that in control group (70.3% *vs.* 48.4%, p=0.012). The possible reason is that interventional chemoembolization keeps a high local drug concentration in the feeding artery of tumors, and also embolizes bilateral uterine arteries in patients, after which acute ischemia and hypoxia are caused in cervical cancer tissues, resulting in tumor tissue necrosis and tumor shrinkage [19,20]. The follow-up results manifested that the 3-year OS was 70.3% (45/64) and 73.4% (47/64), and the 3-year PFS was 64.1% (41/64) and 65.6% (42/64), respectively, in UAIC group and control group. OS and PFS had no statistically significant differences between the two groups (p=0.618, p=0.785). It was discovered that neither interventional chemoembolization nor intravenous chemotherapy combined with intensity-modulated radiotherapy had a significant effect on the long-term survival status and tumor progression in patients. In terms of adverse reactions, there were more cases of pelvic pain during treatment in UAIC group than control group (p=0.015), while UAIC group had fewer cases of myelosuppression, gastrointestinal reactions, liver-kidney damage, alopecia or neurotoxicity than control group (p<0.05). The main reason is that interventional embolization of bilateral uterine arteries is likely to cause pelvic pain, while the drug dosage in interventional chemotherapy is lower, so fewer chemotherapy-related adverse reactions are caused.

In the functional scales of EORTC-QLQ-C30, the scores of physical function, role function, cognitive function, emotional function and social function were higher in UAIC group than those in control group, but only the emotional function score had a statistically significant difference (p=0.040). In the symptom scales, the scores of Sleep disturbance, nausea and vomiting, pain and fatigue were obviously lower in UAIC group than those in control group (p<0.05), while other symptom scores had no statistically significant differences (p>0.05). The possible reason is that due to a lower drug dosage in interventional chemotherapy, fewer chemotherapy-related adverse reactions are caused, and patients' emotion and symptoms are less affected.

In this retrospective study, there was a certain bias in data, the sample size was small and the follow-up period was limited. Therefore, the conclusion made remains to be further verified through multi-center prospective randomized controlled studies in the future, so as to provide a reliable basis for the treatment of mid-advanced cervical cancer.

Conclusions

UAIC combined with radiotherapy has better short-term clinical efficacy than intravenous chemotherapy combined with radiotherapy in the treatment of mid-advanced cervical cancer, with fewer adverse reactions and higher quality of life, but it has no significant effect on the long-term survival and tumor progression in patients.

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Conflict of interests

The authors declare no conflict of interests.

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