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*Original Article*

# Application of vincristine and cisplatin combined with intensity-modulated radiation therapy in the treatment of patients with advanced cervical cancer

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**Abstract:** Objective: To investigate the effect of vincristine and cisplatin combined with intensity-modulated radiation therapy (IMRT) on the treatment of patients with advanced cervical cancer and its influence on adverse reactions. Methods: In this retrospective clinical trial, 90 patients with advanced cervical cancer admitted to our hospital from January 2019 to January 2020 were collected as research subjects and were divided into two groups according to different treatment methods. The control group received IMRT, and the experimental group was treated with a triple therapy of vincristine, cisplatin, and IMRT. The clinical efficacy, incidence of adverse reactions, immune function indexes, serum indexes, and 3-year survival were compared between the two groups. The Generic Quality of Life Inventory-74 (GQOLI-74) questionnaire was used to assess the quality of life, and the Karnofsky Performance Scale (KPS) was used to evaluate the health status. Results: The experimental group exhibited a significantly higher total clinical treatment efficacy in comparison with the control group ($P<0.05$). Patients in the experimental group experienced fewer adverse reactions and better immune indexes as compared to those in the control group (all $P>0.05$). The serum indexes of the experimental group were significantly lower than those of the control group ($P<0.05$). Significantly higher GQOLI-74 scores and KPS scores were obtained in the experimental group than the control group after treatment (all $P<0.05$). The 3-year overall survival rate of the experimental group was significantly higher than that of the control group ($P<0.05$). Conclusion: Vincristine and cisplatin combined with IMRT for patients with advanced cervical cancer can effectively optimize the clinical indicators of patients and improve their quality of life, with a high safety.

**Keywords:** Vincristine, cisplatin, intensity-modulated radiation therapy, advanced cervical cancer

## Introduction

Cervical cancer is a common malignant tumor in gynecology, with a predilection for women aged 50-55 years old [1, 2]. Cervical cancer originates from the cervix. Its etiology is mainly related to human papillomavirus infection. Clinical manifestations of the disease include abnormal vaginal discharge and contact bleeding [3]. Symptoms in the early stage of cervical cancer are rather hidden, which becomes observable after disease progression. In recent years, the incidence of cervical cancer has witnessed an increase, seriously endangering the life of patients and compromising their quality of life [4, 5]. At present, the surgery is the mainstay of clinical treatment for early cervical cancer. However, most of the patients are in the advanced stages at first diagnosis due to its insidious early symptoms, which usually leads to the mis-diagnosis and missing of the best treatment time [6-8]. In addition, the disease may invade and metastasize to other organs and tissues in advanced stages, resulting in anemia, fatigue, and frequent urination. Delayed or ineffective treatment may predispose the patients to a cascade of complications such as vesico-vaginal fistula and vaginal empyema, which seriously endangers the life of patients and lowers their quality of life [9]. Intensity-modulated radiation therapy (IMRT) is an emerging radiotherapy modality that maximizes the concentration of radioactive dose in the lesions, which kills tumor cells while sparing or protecting surrounding normal tissues and organs from unnecessary irradiation [10]. To

the best of our knowledge, notwithstanding a certain clinical effect, the monotherapy of IMRT fails to achieve a satisfactory efficiency, and its combination with vincristine and cisplatin chemotherapy has been reported to potentiate the clinical efficacy [11]. Accordingly, 90 patients with advanced cervical cancer admitted to our hospital from January 2019 to January 2020 were selected to evaluate the application value of vincristine and cisplatin combined with IMRT in the treatment of advanced cervical cancer and the impact on adverse reactions.

## Materials and methods

### *General information*

In this retrospective study, 90 patients with advanced cervical cancer admitted to our hospital from January 2019 to January 2020 were selected and divided into the control group and the experimental group according to the different treatment methods. The control group received IMRT, and the experimental group was treated with a triple therapy of vincristine, cisplatin, and IMRT. This study was approved by the hospital ethics committee with the approved no. of CA 2018-12/345.

### *Inclusion criteria*

(1) Patients who met the diagnostic criteria [12] of cervical cancer without distant metastasis as confirmed by imaging examination; (2) Patients confirmed as middle-advanced cervical cancer; (3) Patients with at least one measurable tumor.

### *Exclusion criteria*

(1) Patients with other malignant tumors; (2) Patients with allergies to the study medication; (3) Patients with dysfunction of heart, liver, kidney, and other vital organs.

The patients were informed of the purpose and process of this study and signed the informed consent form.

### *Methods*

The control group received IMRT alone. On the day of examination, patients were instructed to empty the rectum and take diatrizoate meglumine orally. Computed tomography (CT) scans were performed on patients, from the lower edge of the second lumbar vertebrae to the lower edge of the obturator foramen. The gross tumor volume, clinical target volume, and planning target volume were contoured based on CT images. The planning target volume was located in an area 0.5 cm outside the clinical target volume. The gross tumor volume radiation dose was 50.3 Gy-56 Gy, and the planning target volume was 49.8 Gy-50 Gy. The irradiation was completed in 27 times. When the dose was 40 Gy, the patients were treated with afterload reduction therapy, 6 Gy/time, for 4 times.

The experimental group received vincristine and cisplatin chemotherapy on the basis of the control group. The specific measures were as follows: IMRT was performed the same as the control group. Patients were given intravenous injection of 1.4 mg/m$^2$ vincristine (manufacturer: Shanxi Zhendong Taisheng Pharmaceutical Co., Ltd.; SFDA Approval Number: H140-20811; Specification: 1 mg), 1 time/d. An intravenous infusion of 20 mg/m$^2$ cisplatin (manufacturer: Yunnan Botanical Pharmaceutical Co., Ltd.; SFDA Approval Number: H53021740; Specification: 2 mL: 10 mg) dissolved in 300-500 mL sodium chloride injection dilution was given once daily.

Patients in both groups were treated for 2 months.

All the above treatments were carried out in our hospital, and the flow chart is shown in **Figure 1**.

### *Outcome measures*

Clinical efficacy: Complete response (CR) - the clinical symptoms disappeared for more than 4 weeks; Partial response (PR) - tumor diameter reduced by >50% for more than 4 weeks; Stable disease (SD) - tumor diameter reduced by <50% without the appearance of new lesions; Progressive disease (PD) - new lesions or an increased tumor diameter occurred. The total clinical efficacy = CR+PR.

Incidence of adverse reactions: Adverse reactions including gastrointestinal reactions, liver and kidney dysfunction, bone marrow suppression, and radiation enteritis were compared between the two groups.

Immune function indexes: Fasting venous blood was drawn from patients in both groups and 2 mL blood samples were anticoagulated with ethylenediaminetetraacetic acid, for the determination of CD3+, CD4+, and CD4+/CD8+ of

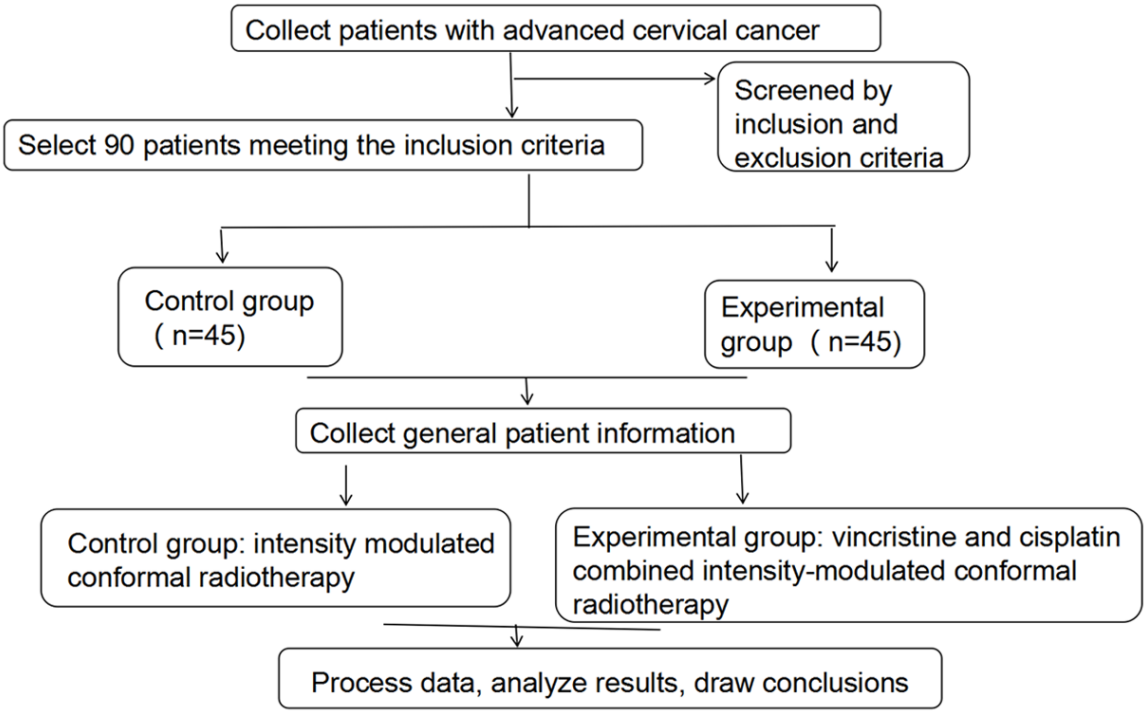


**Figure 1.** Technical roadmap.

T lymphocyte subsets using a flow cytometry (manufacturer: Partec, Germany; model CyFlow® Ploidy Analyser).

Fasting morning cubital venous blood was drawn from all the patients and centrifuged to obtain the serum. All serum samples were stored at -80°C. The levels of CA125 and CA199 were determined using the ELISA.

Quality of life: The Generic Quality of Life Inventory-74 (GQOLI-74) questionnaire [13] was used to evaluate patients' quality of life after treatment. The scale is scored from four dimensions of mental function, physical function, social function, and material life status, with a total score of 100 points. The higher the score, the better the quality of life.

Health status: The Karnofsky Performance Scale (KPS) [14] was used to evaluate the health status of the two groups of patients. The higher the KPS score, the better the health status, the more tolerant of the side effects of the treatment, and therefore the higher the possibility of a radical cure. 100 points: Patients were normal and asymptomatic. 90 points: Patients can perform normal activities with mild signs and symptoms. 80 points: Patient can barely perform normal activities with some signs or symptoms. 70 points: Patients can take care of themselves but cannot maintain a normal life and work. 60 points: Patients can mostly take care of themselves, with occasional assistance from others. 50 points: Patients with frequent assistance in daily life. 40 points: Patients cannot take care of themselves and need special care and assistance. 30 points: Patients with little self-care ability. 20 points: Patients are seriously ill and require hospitalization and aggressive supportive care. 10 points: Patients in critical condition, dying. 0 points: Death. A score below 60 prevents the implementation of many effective anti-tumor treatments.

The patients were followed up by visiting outpatient clinic or telephone, and the three-year survival was calculated.

*Statistical analysis*

The processing software SPSS20.0 was used for data analysis, and GraphPad Prism 7 (GraphPad Software, San Diego, USA) for graphics plotting. The measurement data were expressed as mean ± SD, and the intra-group comparison was conducted using Paired t test while the inter-group comparison was conducted using independent-samples t test. Count

**Table 1.** Comparison of general information between the two groups

| | Experimental group (n=45) | Control group (n=45) | $x^2$ or t | P |
|---|---|---|---|---|
| Age (year) | 66.25±3.32 | 66.33±3.29 | 0.115 | 0.909 |
| BMI (kg/m$^2$) | 26.27±1.59 | 25.89±1.63 | 1.119 | 0.266 |
| Mean tumor diameter (cm) | 3.01±1.21 | 3.02±1.11 | 0.041 | 0.968 |
| SAS (point) | 47.33±0.51 | 47.17±0.48 | 1.533 | 0.129 |
| SDS (point) | 52.13±1.61 | 52.21±1.32 | 0.258 | 0.797 |
| Clinical staging | | | 0.182 | 0.670 |
| IIIb | 18 (40.00) | 20 (44.44) | | |
| IV | 27 (60.00) | 25 (55.56) | | |
| Tumor typing | | | | |
| Squamous cell carcinoma | 28 (62.22) | 29 (64.44) | 0.048 | 0.827 |
| Adenocarcinoma | 10 (22.22) | 11 (24.44) | 0.062 | 0.803 |
| Adenosquamous carcinoma | 7 (15.56) | 5 (11.11) | 0.385 | 0.535 |
| Place of residence | | | 0.050 | 0.822 |
| Town | 31 (68.89) | 30 (66.67) | | |
| Rural area | 14 (31.11) | 15 (33.33) | | |

data were expressed as n (%) and analyzed using the chi-square test. *P* values <0.05 were considered as statistically significant.

## Results

*Comparison of general information*

There were no significant differences in age, BMI, average tumor diameter, SAS score, SDS score, tumor clinical stage, tumor type, and place of residence between the two groups (P>0.05), as shown in **Table 1**.

*Comparison of clinical efficacy between the two groups*

The experimental group obtained a significantly higher total clinical efficacy after treatment in comparison with the control group (P<0.05), as shown in **Table 2**.

*Comparison of the incidence of adverse reactions between the two groups*

As shown in **Table 3**, the experimental group experienced fewer adverse reactions as compared to the control group (P>0.05).

*Comparison of immune indicators between the two groups*

After treatment, the immune indexes of the experimental group were significantly better than those of the control group (P<0.05), as shown in **Table 4**.

*Comparison of serum indexes between the two groups*

After treatment, the serum indexes of the experimental group were significantly lower than those of the control group (P<0.05), as shown in **Table 5**.

*Comparison of GQOLI-74 scores between the two groups*

Regarding patients' quality of life, the GQOLI-74 score of the experimental group was significantly higher than that of the control group after treatment (P<0.05), as shown in **Table 6**.

*Comparison of KPS scores between the two groups*

The experimental group was superior to the control group in KPS scores after treatment (P<0.05), as shown in **Figure 2**.

*Comparison of the long-term survival rate between the two groups*

The results showed that the median survival time of patients in the experimental group was 26 months, and 41 cases survived, with a survival rate of 88.89% (40/45). The median survival time of patients in the control group was 23 months, and 27 cases survived, with a survival rate of 57.78% (26/45). The results indicated that the 3-year overall survival rate of the experimental group was significantly higher than that of the control group (P<0.05), as shown in **Figure 3**.

## Discussion

In this study, both treatment methods implemented in the two groups achieved remarkable therapeutic effects, with a higher response rate in the experimental group, indicating that the combined therapy of vincristine, cisplatin, and IMRT outperformed monotherapy. Clini-

**Table 2.** Comparison of clinical efficacy between the two groups [n (%)]

| Groups | n | CR | PR | SD | PD | Total effectiveness |
|---|---|---|---|---|---|---|
| Experimental group | 45 | 22.22% (10/45) | 37.78% (17/45) | 17.78% (8/45) | 22.22% (10/45) | 60.00% (27/45) |
| Control group | 45 | 6.67% (3/45) | 15.56% (7/45) | 31.11% (14/45) | 46.67% (21/45) | 2.22% (10/45) |
| $x^2$ | | | | | | 13.264 |
| P | | | | | | <0.001 |

**Table 3.** Comparison of the incidence of adverse reactions between the two groups [n (%)]

| Groups | n | Gastrointestinal reaction | Abnormal liver and kidney function | Bone marrow suppression | Radiation enteritis | Total incidence |
|---|---|---|---|---|---|---|
| Experimental group | 45 | 4.44% (2/45) | 4.44% (2/45) | 8.89% (4/45) | 6.67% (3/45) | 24.44% (11/45) |
| Control group | 45 | 6.67% (3/45) | 6.67% (3/45) | 11.11% (5/45) | 8.89% (4/45) | 33.33% (15/45) |
| $x^2$ | | | | | | 0.865 |
| P | | | | | | 0.352 |

**Table 4.** Comparison of immune indicators between the two groups ($\bar{x}\pm s$)

| Groups | n | CD3+ (%) | | CD4+ (%) | | CD4+/CD8+ | |
|---|---|---|---|---|---|---|---|
| | | Before therapy | After therapy | Before therapy | After therapy | Before therapy | After therapy |
| Experimental group | 45 | 70.66±8.15 | 79.23±9.21 | 55.88±6.27 | 63.21±6.85 | 1.27±0.31 | 1.52±0.41 |
| Control group | 45 | 70.67±8.21 | 49.27±6.11 | 55.86±6.25 | 46.01±5.93 | 1.28±0.32 | 1.15±0.16 |
| t | | 0.006 | 19.731 | 0.015 | 12.735 | 0.151 | 5.639 |
| P | | 0.995 | <0.001 | 0.988 | <0.001 | 0.881 | <0.001 |

**Table 5.** Comparison of serum indexes between the two groups ($\bar{x}\pm s$)

| Groups | n | CA125 | | CA199 | |
|---|---|---|---|---|---|
| | | Before therapy | After therapy | Before therapy | After therapy |
| Experimental group | 45 | 68.88±11.21 | 44.36±8.01 | 38.88±1.35 | 11.25±1.27 |
| Control group | 45 | 68.75±11.35 | 56.93±7.35 | 38.79±1.41 | 29.86±1.31 |
| t | | 0.055 | 7.756 | 0.074 | 68.422 |
| P | | 0.957 | <0.001 | 0.941 | <0.001 |

**Table 6.** Comparison of GQOLI-74 scores between the two groups ($\bar{x}\pm s$)

| Groups | n | Mental function | Physical function | Social function | State of material life |
|---|---|---|---|---|---|
| Experimental group | 45 | 82.35±5.8 | 83.27±5.9 | 83.56±6.8 | 84.52±7.9 |
| Control group | 45 | 63.32±4.7 | 62.12±4.9 | 65.32±5.7 | 65.23±5.8 |
| t | | 17.908 | 18.499 | 13.789 | 13.203 |
| P | | <0.001 | <0.001 | <0.001 | <0.001 |

cally, radiotherapy and chemotherapy are mainly used in the middle and advanced stages, but neither obtains satisfactory outcomes in the inhibition of the metastasis and spread of tumors [15]. IMRT controls the intensity distribution of radiation, increases the radiation dose in the tumor area, and reduces the radiation dose in adjacent tissues, which has huge advantages over conventional radiotherapy [16]. However, it was clinically found that the efficacy of single treatment remains unsatisfactory, with a mediocre survival rate, for which, the introduction of vincristine and cisplatin chemotherapy may potentiate the therapeutic effect. Vincristine is a widely used anti-tumor drug that effectively inhibits the polymerization of

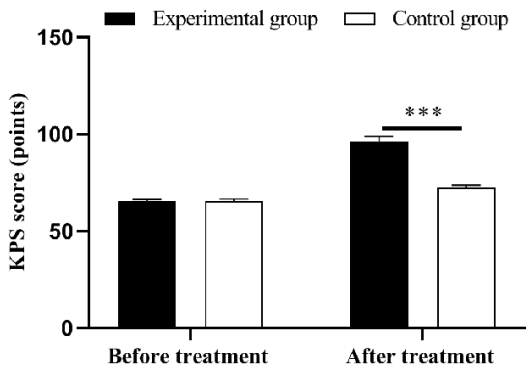


**Figure 2.** Comparison of KPS scores. Note: ***, P<0.001.

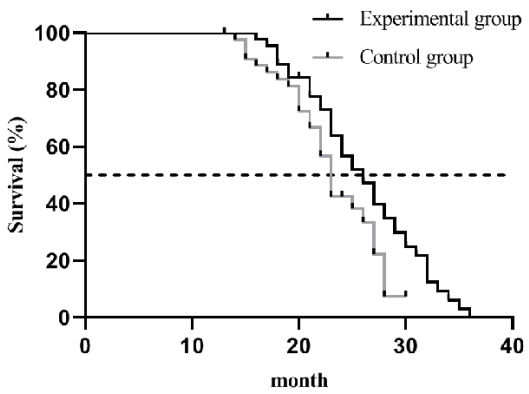


**Figure 3.** Comparison of long-term survival rates between the two groups.

tubulin and affects the formation of spindle microtubules. Additionally, it has been reported to inhibit the activity of RNA polymerase and the synthesis of cell membrane lipids, and interfere with protein metabolism [17, 18]. Furthermore, cisplatin substantially suppresses DNA replication in tumor cells and destroys the structure of tumor cell membranes.

The present study showed that the immune indicators of the experimental group were significantly better than those of the control group after treatment, suggesting that the immune function of patients remains intact after the application of the combined therapy of vincristine, cisplatin, and IMRT. To the best of our knowledge, elderly patients with cervical cancer are less resistant and more vulnerable to chemotherapy which may impair their immune function. Related studies have found that T lymphocytes play a key role in the development and progression of tumors. Among them, CD3 refers to mature T lymphocytes, which can reflect the overall immune function, CD4 is a kind of inducible T cells, which is the primary hub cell in regulating immune response, CD8 refers to suppressor T cells, which can effectively inhibit the spread and replication of viruses, and kill tumor cells and human cells infected by viruses, and CD4/CD8 is an major sensitive index to judge immune dysfunction [19, 20]. As one of the key serum markers in cervical cancer, CA125 is closely related to the development of a variety of tumors. CA199, isolated from colon cancer cells, is strongly associated with digestive system tumors such as pancreatic cancer and liver cancer. The present study found that the serum indexes of the experimental group were significantly lower than those of the control group after treatment, suggesting that vincristine and cisplatin combined with IMRT effectively lower the expression levels of tumor markers.

It is worth noting that the 3-year overall survival rate of the experimental group was significantly higher than that of the control group, indicating that vincristine and cisplatin combined with IMRT prolong the survival time of patients. The experimental group was superior to the control group with respect to the GQOLI-74 score and KPS score after treatment. All these confirmed that the health status and quality of life of cancer patients have obtained substantial improvement after receiving vincristine and cisplatin combined with IMRT. Previous research has pointed out that single radiotherapy is inferior to the combination therapy with multiple drugs in prolonging survival and further optimizing the clinical efficacy of patients with advanced cervical cancer. Interestingly, the two groups showed no difference in the total incidence of adverse reactions, which was in line with the results of ZHU YINGPING et al. [21] who also reported that the adverse reactions rate in both groups was not statistically different (55.55% vs 60.00%), demonstrating that the triple therapy of vincristine, cisplatin, and IMRT and multi-drug therapy have a higher safety.

## Conclusion

Overall, the combination of vincristine and cisplatin and IMRT in patients with advanced cervical cancer is a preferable technique in terms

of boosting the quality of life and improving the clinical indicators of patients, with high safety, which is worthy of clinical promotion and application.

## Disclosure of conflict of interest

None.

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