

Effect of Internal Iliac Artery Embolization Combined With Arterial Infusion Chemotherapy On Serum VEGF, HGF and IL-6 in Advanced Cervical Cancer

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This study aimed to investigate the effect of internal iliac artery embolization combined with arterial infusion chemotherapy on serum VEGF, HGF and IL-6 in advanced cervical cancer. A total of 120 cases of patients with advanced cervical cancer and admitted to Binzhou Center Hospital from January 2014 to March 2016 were selected as research subjects. Among them, 59 patients received arterial infusion chemotherapy were enrolled in the control group, and 61 patients received arterial infusion chemotherapy combined with internal iliac artery embolization were included in the observation group. Treatment efficacy, serum VEGF, HGF and IL-6 expression, KPS score and QOL score, incidence of adverse reactions and 3-year survival rate of the two groups were recorded and compared. The result showed that the therapeutic effect of the observation group was significantly higher than that of the control group ($P < 0.05$). The expression of serum VEGF, HGF and IL-6, KPS score and QOL score in the two groups were significantly improved after treatment, with more significant improvement in the observation group ($P < 0.05$). There were no significant differences in the incidence of adverse reactions between the two groups ($P > 0.05$). And the 3-year survival rate of the observation group was significantly higher than that of the control group ($P < 0.05$). In conclusion, arterial infusion chemotherapy combined with internal iliac artery embolization has a better effect than arterial infusion chemotherapy alone in treating patients with advanced cervical cancer. It can effectively prolong the survival of patients, along with good safety, which is worthy of clinical promotion.

Keywords: internal iliac artery embolization, arterial infusion chemotherapy, advanced cervical cancer, VEGF, HGF, IL-6

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As a malignant tumor with high incidence, cervical cancer has a high mortality rate. In recent years, with the change of social environment, its incidence is also getting higher and younger^{1,2}. Advanced cervical cancer generally refers to the patients with cervical cancer of grade I_{b2}-IV_a. In this period of disease, even though numerous patients have received surgical treatment, due to the highly invasive nature of advanced cervical cancer, however, they will suffer from poor

prognosis and poor efficacy^{3,4}. Current clinical treatment experience of cervical cancer shows that the preoperative chemoradiotherapy can provide certain conditions for the operation of patients⁵. Although traditional chemoradiotherapy has a certain curative effect, it can bring about serious adverse reactions and damage to the patient's body, which does harm to patient's surgical endurance⁶. Therefore, it is of great clinical significance to find a treatment method that can effectively treat

cervical cancer patients and produce minor adverse reactions.

Arterial infusion chemotherapy is a commonly used neoadjuvant chemotherapy in clinical practice. As a safe and less invasive treatment method, it has a good clinical effect. Its main principle is to introduce special catheter and guide wire and other instruments into the human body through the guidance of imaging equipment, so as to conduct local treatment of tumors in vivo^{7,8}. Internal iliac artery embolization is also a commonly used tumor treatment method in clinical practice in recent years. It mainly embolizes the blood vessels at the lesion site, resulting in necrosis of the tumor tissue, thus achieving the purpose of treatment⁹. However, there are few studies on the application of internal iliac artery embolization combined with arterial infusion chemotherapy in cervical cancer.

In order to provide more options for the treatment of advanced cervical cancer, we investigated the efficacy of internal iliac artery embolization combined with arterial infusion chemotherapy in the treatment of advanced cervical cancer, and specifics were as follows.

DATA AND METHODS

General Data

Prospective analysis was performed on 120 patients with advanced cervical cancer admitted to Binzhou Center Hospital from January 2014 to March 2016. The average age of all patients was (46.7±2.3) years. Among them, 59 patients who received arterial infusion chemotherapy were enrolled in the control group, and 61 patients who received arterial infusion chemotherapy combined with internal iliac artery embolization were included in the observation group. Patients whose advanced cervical cancer diagnosed by pathology and patients with an estimated survival of more than 6 months were enrolled in the study. Exclusion criteria were as follows: Patients complicated with other malignant tumors, distant metastasis, severe liver and kidney dysfunction. Patients who had received chemotherapy previously. Patients who did not cooperate with treatment. Patients with chemotherapy intolerance. All

patients and their families have agreed to participate in the experiment and signed informed consent. This study has been approved by the ethics committee of Binzhou Center Hospital.

Therapies

Patients in both groups were treated with arterial infusion chemotherapy firstly. The procedure were as follows: first, local anesthesia was given to the patient, then 5F catheter was placed and inserted into the internal iliac artery through right femoral artery puncture under digital subtraction angiography, and then, contrast agent was injected. When the blood supply distribution of the tumor was determined, cisplatin (40mg) and fluorouracil (1000mg) were injected through the catheter, followed by continuous treatment for 5d. The treatment was conducted at an interval of 2d, with one course of treatment of 21d and two courses in a treatment. On the basis of arterial infusion chemotherapy, patients in the observation group were treated with internal iliac artery embolization. The specific operation procedure was as follows: after patients received arterial infusion chemotherapy, gelfoam particles were mixed with contrast agent and slowly injected into the most obvious branch of the tumor that supplying blood. Completely stopped arterial blood flow indicated successful embolization. After extubation, the puncture site was performed with pressure dressing, and the treatment course was the same as arterial infusion chemotherapy.

Index Detection

Venous blood (5ml) was extracted from the patients before and after the treatment. After centrifugation at a speed of 250xg/min, the supernatant was taken for detection. The expression of serum vascular growth factor (including VEGF-A, VEGF-C and VEGF-D), hepatocyte growth factor (HGF) and interleukin-6 (IL-6) were detected by ELISA. The detection was carried out strictly in accordance with the operation instructions of ELISA kit.

Observational Indexes

(1) After the completion of the course of treatment, the therapeutic efficacy of patients in the two groups was evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST) ¹⁰, which were divided into complete response, partial response, stable disease and progressive disease. The total effective rate of treatment = (complete response + partial response) / total number of patients x 100%. (2) Serum VEGF, HGF and IL-6 of the two groups were detected and compared before and after treatment. (3) Karnofsky performance status (KPS) ¹¹ and quality of life (QOL) ¹² of patients in the two groups after 3 months of treatment were evaluated and compared. The total QOL score is 60 points, 51 to 60 points means excellent quality of life, 41 to 50 points means good quality of life, 31 to 40 points means average quality of life, 21 to 30 points means poor quality of life, and below 20 points means poor quality of life. (4) Adverse reactions occurred during treatment in both groups were recorded and compared, including fever, nausea and vomiting, platelet decline and leukocyte decline. (5) Patients

in the two groups were followed up for 36 months by WeChat, telephone or outpatient service, and the death and survival rates of the patients in the two groups within 3 years were recorded.

Statistical Methods

In this study, SPSS19.0 software (Bizinsight (Beijing) information technology Co., Ltd.) was used for statistical analysis of experimental data, enumeration data was qualified by chi-square test, and measurement data was expressed by mean ± standard deviation. Comparison between the two groups was qualified by t test, and comparison before and after treatment was qualified by paired t test. GraphPad Prism 6 software was used to draw pictures of this experiment. $P < 0.05$ was regarded as statistically significant.

RESULTS

General Data

There was no significant difference between the two groups in age, BMI, pathological type, etc. ($P > 0.05$), suggesting comparability. More details were shown in Table 1.

Table 1.
Comparison of general data

Factors	Observational group n=61	Control group n=59	t/X ²	P
Age (years old)	46.36±2.18	46.86±2.34	1.212	0.228
BMI(kg/m ²)	22.46±2.13	22.68±2.17	0.560	0.576
Procreate or not			0.119	0.730
Yes	54 (88.52)	51 (86.44)		
No	7 (11.48)	8 (13.56)		
Accompanied by HPV or not			0.175	0.675
Yes	58 (95.08)	57 (96.61)		
No	3 (4.92)	2 (3.39)		
Pathological pattern			0.285	0.867
Adenocarcinoma	22 (36.07)	20 (33.90)		
Squamous carcinoma	24 (39.34)	26 (44.07)		
Adenosquamous carcinoma	15 (24.59)	13 (22.03)		
Pathological stage			0.345	0.558
I _b -II _b	34 (55.74)	36 (61.02)		
III _a -IV _a	27 (44.26)	23 (38.98)		

Comparison of Therapeutic Effect of Patients in the Two Groups

The number of patients in the observation group with complete response, partial response, stable disease and progressive disease after treatment was 10, 37, 12 and 1, respectively, with a total effective rate of treatment of 77.05%. The

number of patients in the control group with complete response, partial response, stable disease and progressive disease after treatment was 2, 24, 15 and 8, respectively, with a total effective rate of treatment of 61.02%. The total effective rate of the observation group was significantly higher than that of the control group ($P < 0.05$). More details

were shown in Table 2.

Table 2.
Comparison of therapeutic effect of patients in the two groups

Curative effect	Observation group n=61	Control group n=59	X ²	P
Complete response	10 (16.39)	2 (3.39)	5.635	0.018
Partial response	37 (60.66)	24 (40.68)	4.789	0.029
Stable disease	12 (19.67)	15 (25.42)	0.569	0.451
Progressive disease	1 (1.64)	8 (13.56)	6.143	0.013
Total effective rate	47 (77.05)	36 (61.02)	4.228	0.040

Expression of Serum VEGF, HGF and IL-6 of Patients in the Two Groups

Before treatment, there was no significant difference in serum VEGF-A, VEGF-C, VEGF-D, HGF and IL-6 expression in the two groups (P>0.05). After treatment, the serum VEGF-A,

VEGF-C, VEGF-D, HGF and IL-6 expression in the two groups were significantly lower than those before treatment, but the decrease was more significant in the observation group (P<0.05). The difference was statistically significant (Figure 1).

Figure 1.
Expression of serum VEGF, HGF and IL-6 in the two groups

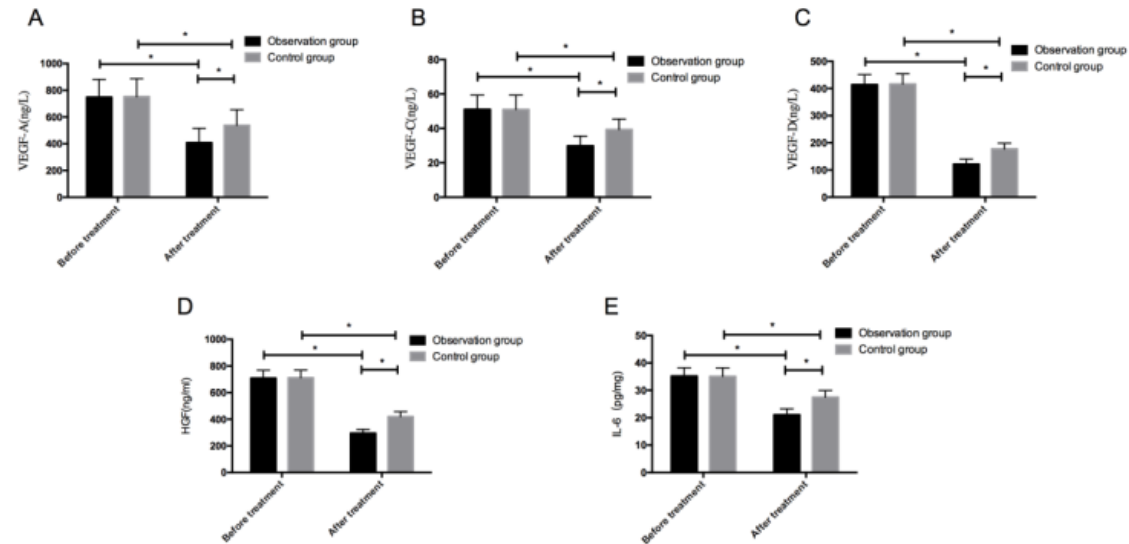


Figure A: Expression of serum VEGF-A. Figure B: Expression of serum VEGF-C. Figure C: Expression of serum VEGF-D. Figure D: Expression of serum HGF. Figure E: Expression of serum IL-6. * means P<0.05.

Comparison of KPS and QOL Scores between the Two Groups before and after 3 Months of Treatment

There were no significant differences in the KPS and QOL scores between the two groups before treatment (P>0.05). After treatment, the KPS and

QOL scores of the two groups were significantly improved, but the improvement of the observation group was more obvious than that of the control group (P<0.05). More details were shown in Figure 2.

Figure 2.

Comparison of KPS and QOL scores between the two groups before and after 3 months of treatment

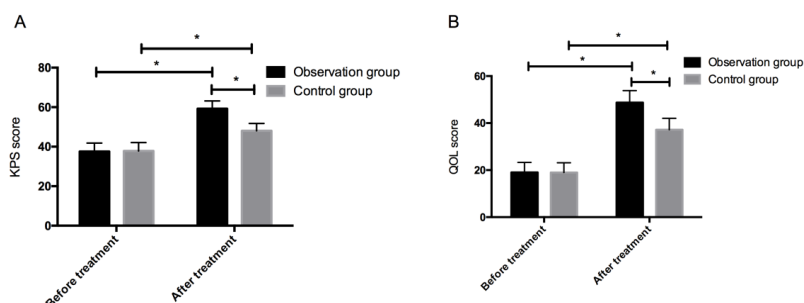


Figure A: Comparison of KPS scores between the two groups before and after 3 months of treatment. Figure B: Comparison of QOL scores between the two groups before and after 3 months of treatment. * means $P < 0.05$.

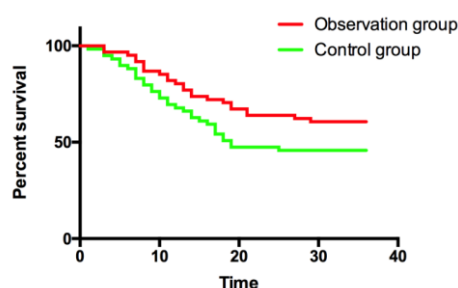
Comparison of Adverse Reactions between the Two Groups

The number of patients in the observation group with fever, nausea and vomiting, decreased platelet count and leukocyte count were 3, 2, 3 and 2, respectively, with the incidence of complications of 16.39%. The number of patients in the control

group with fever, nausea and vomiting, decreased platelet count and leukocyte count were 3, 1, 2 and 2, respectively, with the incidence of complications of 13.56%. There were no significant differences in the incidence of adverse reactions between the two groups ($P > 0.05$). More details were shown in Figure 3.

Figure 3.

Comparison of 3-year survival rate between the two group



A total of 24 patients died in the observation group during the follow-up period, with a 3-year survival rate of 60.66%. While 32 patients died in the control group during the follow-up period, with a 3-year survival rate of 47.54%. The 3-year

survival rate of the observation group was significantly higher than that of the control group, with statistically significant differences ($P < 0.05$). More details were shown in Figure 3.

DISCUSSION

As a common malignant tumor of female reproductive system, cervical cancer has always developed to local advanced stage when patients receive treatment, which is not suitable enough for surgical treatment¹³. For patients with advanced cervical

cancer, the curative effect of surgical treatment is not ideal for high postoperative local recurrence rate of the tumor and unsatisfactory prognosis¹⁴. At present, adjuvant chemotherapy is a popular treatment method in the treatment of cervical

cancer, and the efficacy of arterial infusion chemotherapy combined with internal iliac artery embolization was also assessed in our study.

As the most important route of neoadjuvant chemotherapy at present, arterial infusion chemotherapy can make the concentration of drugs in local tumor tissues three times higher than that of intravenous chemotherapy drugs, improving the killing ability of drugs on tumors significantly. It can also reduce the distribution of drugs in the normal systemic circulation, thus improving the adverse reactions of patients¹⁵. In this case, every patient in our study was treated with arterial infusion chemotherapy. In order to further explore the efficacy of internal iliac artery embolization combined with arterial infusion chemotherapy, however, we added internal iliac artery embolization on the basis of arterial infusion chemotherapy in the observation group. The results showed that the therapeutic effect of the observation group was better than that of the control group. Previous studies¹⁶ have pointed out that internal iliac artery embolization is mainly a method accelerating the necrosis of tumor cells by blocking the blood supply and nutrient supply of tumor tissues. It has a good effect on tumor treatment, which is consistent with our conclusions. VEGF is an angiogenesis factor secreted by malignant cells, which can stimulate the formation of abnormal blood vessels and lymphatic vessels. High expression of VEGF plays an important role in the occurrence and development of tumors¹⁷. As a polypeptide growth factor, HGF has a strong promoting effect on cell division and can also induce cell invasion and migration¹⁸. As an inflammatory factor, IL-6 has a variety of functions. Previous studies have pointed out that tumor cells can secrete IL-6 themselves, and IL-6 can promote the metastasis of tumor cells by acting together with various factors⁽¹⁹⁾. Subsequently, in order to further understand the effect of arterial infusion chemotherapy combined with internal iliac artery embolization on patients, we observed that the expression of serum VEGF-A, VEGF-C, VEGF-D, HGF and IL-6 in both groups were significantly

decreased after treatment compared with that before treatment, indicating that arterial infusion chemotherapy had a good effect on patients with advanced cervical cancer. What's more, the improvement of these indicators in the observation group was more obvious than that in the control group, which indicated that arterial perfusion chemotherapy combined with internal iliac artery embolization had better inhibitory effect on the expression of serum VEGF, HGF and IL-6. In the past, the efficacy evaluation of arterial infusion chemotherapy combined with internal iliac artery embolization in the treatment of cervical cancer was mostly conducted by pathological analysis²⁰, but the changes in the expression of serum VEGF, HGF and IL-6 may provide a new way of efficacy evaluation, which can reduce the pain of patients.

Then we evaluated the impact of these two treatment methods on patients from the aspects of function and quality of life of patients. KPS score is a score which can be used to assess the physical health status of tumor patients, and the higher the score, the better the patient's tolerance to treatment²¹. QOL score is an indicator that can assess the quality of life of tumor patients²². The results of our study showed that the KPS score and QOL score of the patients in the observation group after 3-month treatment were significantly higher than those in the control group, which indicated that the treatment with arterial perfusion chemotherapy combined with internal iliac artery embolization had better effect on the postoperative recovery of the patients. Then we also evaluated the adverse reactions of the two groups of patients during treatment, and the results showed that there were no significant differences in the incidence of adverse reactions between the two groups of patients, suggesting that the combination of internal iliac artery embolization on the basis of arterial infusion chemotherapy would not aggravate the adverse reactions and had a higher safety. And patients in the observation group had a higher 3-year survival rate than patients in the control group, indicating that arterial infusion

chemotherapy combined iliac artery embolization could be effective in improving the long-term survival of patients. However, since our follow-up was only 36 months, long-term 5-year survival still requires further follow-up.

In conclusion, arterial infusion chemotherapy combined with internal iliac artery embolization has better efficacy in patients with advanced cervical cancer than arterial infusion chemotherapy alone. It can effectively improve the survival rate of patients, along with good safety, which is worthy of clinical promotion. However, there are some deficiencies in this study. For example, we did not compare arterial infusion chemotherapy with traditional chemotherapy. In addition, VEGF, HGF and IL-6 are indicators reflecting different aspects of the body, and their clinical application value is still unclear, which requires more data to support their clinical value in cervical cancer. Last, due to the insufficient sample size, our conclusions may be inaccurate to some extent, but we will further increase the sample size for further analysis in future studies.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

AUTHORS' CONTRIBUTIONS

HC wrote the manuscript, analyzed and interpreted the patient general data. KW performed ELISA. TY was responsible for observation indicators analysis. All authors read and approved the final manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of Binzhou Center Hospital. Patients who participated in this research, signed the informed consent and had complete clinical data. Signed written informed consents were obtained from the patients and/or guardians.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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