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Analysis of Clinical Factors Affecting Radical Radiotherapy for Cervical Cancer

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Abstract

Objective: To investigate the long-term effects, prognostic factors, and radiotherapy complications of radical radiotherapy in cervical cancer patients.

Methods: A total of 855 patients with primary cervical cancer admitted between January 2004 and March 2014 were treated with radical radiotherapy. After three-dimensional conformal radiotherapy (30 Gy to 44 Gy), a bilateral parametrium dose of 46 Gy to 58 Gy was added. Intracervical brachytherapy was conducted simultaneously with external radiation therapy, with 6 Gy to7 Gy per fraction for five to six fractions and an average dose of 32.6 Gy. A total of 132 patients received uterine artery chemoembolization (UACE). Most patients received up to four cycles of systemic chemotherapy.

Results: In all patients, the total Disease-Specific Survival (DSS) in 2, 5, and 10 years was 87.6%, 52.4%, and 30.2% respectively. Cox multivariate analysis showed that the independent prognostic factors affecting survival rate from cervical cancer following radical radiotherapy were age, UACE, clinical stage, Hemoglobin (Hgb) level, systemic chemotherapy, and total dose at location A. Age and total dose at location A and total dose at location B were the risk factors for delayed rectal injury, while clinical stage and total dose at location B were the risk factors for delayed small bowel injury, and UACE was the only risk factor for delayed bladder injury.

Conclusion: Age at onset, Hgb level, systemic chemotherapy, and total dose at location A were positive factors affecting the prognosis of in cervical cancer patients following radical radiotherapy, while clinical stage and interventional therapy were negative factors.

Keywords: Cervical cancer; Radiotherapy; Prognostic factor; Complication

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Introduction

Cervical cancer is one of the most common malignant gynecological tumors. Early-stage cervical cancer is mainly treated with comprehensive therapy based on surgery, while advanced cervical cancer is mostly treated by comprehensive treatment based on radiotherapy. In addition to distant metastasis, local uncontrolled and recurrent primary cervical cancer lesions are causes of treatment failure in cervical cancer. Simple increases in the prescribed doses of radiotherapy cannot significantly improve local control of the disease or the long-term survival rates of patients but increase toxicity and side effects. A large quantity of data confirmed that the prognoses of malignant tumors are affected by various factors. Only by fully understanding the positive or negative effects of various clinical factors in the treatment of cervical cancer can individualized treatment plans be developed.

Materials and Methods

Clinical data

The curative effect of radical radiotherapy on 855 cervical cancer patients admitted to the Cancer Center of Lanzhou General Hospital of Lanzhou Military Region from January 2004 to March 2014 was retrospectively analyzed. The inclusion criteria were as follows: (1) patients with primary cervical

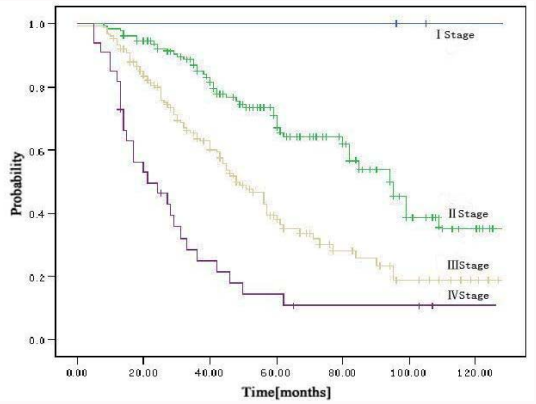

Figure 1: Survival of patients with different FIGO stages.

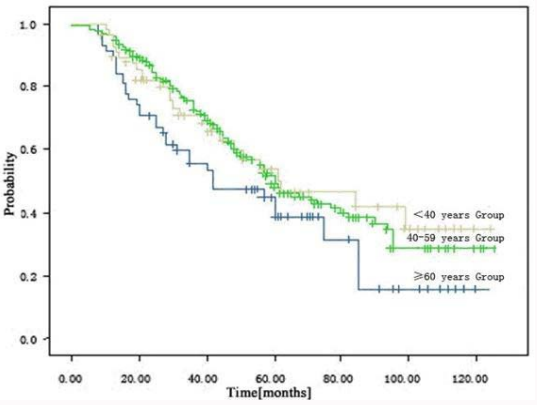

Figure 2: Survival of patients with different age groups.

cancer and pathological type squamous cell carcinoma; (2) patients receiving primary treatment, with no previous anti-tumor treatments including surgery and adjuvant chemotherapy; (3) patients with FIGO stage I to IVa; and (4) patients with no serious primary diseases of the heart, lung, and kidney, and who had completed a radical radiotherapy plan. The exclusion criteria included: (1) cervical cancer patients who are pregnant and/or lactating; (2) patients with other simultaneous or previous primary tumors; (3) patients who failed to complete the radiotherapy plan on schedule (extended treatment longer than 7 days as scheduled); and (4) patients with non-neoplastic death. Patients were aged between 24 and 80 years (mean, 49.9 years; median, 50 years), with 26 cases of FIGO stage I, 354 cases of FIGO stage II, 370 cases of FIGO stage III, and 105 cases of FIGO stage IVa. There were 105 cases with high differentiation, 432 cases with moderate differentiation, and 318 cases with low differentiation. The Hgb levels of all patients measured before treatment were between 52 g/L to 160 g/L, with an average level of 114.6 g/L, and a median level of 121 g/L; among them, there were 162 cases with <90 g/L, 92 with 90 g/L to 99 g/L, 71 with 100 g/L to 109 g/L, 100 with 110 g/L to 119 g/L, and 430 with ≥ 120 g/L (the normal reference range of clinical Hgb in our hospital is 131 g/L to 172 g/L). A total of 132 patients who developed intractable vaginal bleeding underwent uterine artery chemoembolization (UACE). In patients with FIGO stage II to IVa, 684 cases received systemic chemotherapy during radiotherapy.

All patients underwent multi-disciplinary consultation before treatment and gave written informed consent to treatment.

Therapeutic methods

Radiotherapy: All patients completed the following radical radiotherapy treatment planning process (external radiation therapy + intra-cervical brachytherapy). External radiation was administered with 8 MV-X ray three-dimensional conformal radiotherapy (four-field irradiation) at 2 Gy/day for 4 to 5 days/week. The range of exposure include the cervix, vagina, internal and external iliac, and lymphatic drainage regions of the lower segments of common iliac and abdominal aorta (lower margin of L4 spinal segment). Radiation at the lymphatic drainage area of the inguinal lymph node was individualized according to the disease condition (such as vaginal involvement). After external radiation pelvic doses of 30 Gy to 44 Gy, the bilateral parametrium dose was added at 46 Gy to 58 Gy, and the average doses at location A and B were 36.3 Gy and 52.7 Gy, respectively. Intra-cervical brachytherapy was conducted simultaneously with external radiation therapy, with 6 Gy to 7 Gy per fraction for 5 to 6 fractions, and an average dose (location A) of 32.6 Gy. High-dose rate intra-cervical brachytherapy (Ir^{192}) was performed simultaneously with external radiation therapy, with 6 Gy to 7 Gy per fraction for 5 to 6 fractions, once a week; the average dose (location A) was 32.6 Gy. External irradiation was suspended on the day of intracavitary irradiation.

Uterine artery chemoembolization (UACE): Catheterization *via* the right femoral artery was performed using the Seldinger technique, and super-selective arteriography was performed for bilateral internal iliac and uterine tumors. Blood vessels were injected with chemotherapeutic drugs as follows: cisplatin 60 mg/m^2 + fluorouracil 750 mg/m^2 (or bleomycin 60 mg/m^2), bleomycin (60 mg/m^2), cisplatin 60 mg/m^2 + fluorouracil (or bleomycin 60 mg/m^2), lipiodol 5 ml to10 ml [for patients in the UACE group, polyvinyl alcohol (PVA) particles with diameter of 300 μm to 700 μm were selected according to the vascular status of the tumor to embolize bilateral uterine artery, then angiography was performed to evaluate the effect of embolization]. Finally, the guide wire and catheter were removed, and then compression hemostasis and bandaging were performed.

Systemic chemotherapy: With the exception of 171 cases of early-stage disease (stage I), old age (>70 years old), poor general condition (Karnoff score ≤ 70), severe anemia (Hgb ≤ 70 g/L) or personal willingness, 2014 cycles of systemic chemotherapy were performed in the other 684 cases: cisplatin 75 mg/m^2 + paclitaxel 135 mg/m^2, 21 d × 4; cisplatin 70 mg/m^2 + fluorouracil 1,000 mg/m^2/d, 21 d × 4 (the latter was used for patients with paclitaxel allergy). Some patients failed to complete four cycles of synchronous systemic chemotherapy because of toxic reactions such as severe bone marrow suppression and gastrointestinal reactions.

Follow-up and statistical methods

Follow-up observations began from the admission of the patient to the end of radiotherapy, and the follow-up after radiotherapy was carried out by outpatient review and telephone until December 31, 2014; the excluded patients were treated as truncations. SPSS 15.0 software was used for statistical analysis. Disease-Specific Survival (DSS) was analyzed using the Kaplan-Meier method and tested by log-rank method. The clinical data and incidence of complications between groups were related with cross-table comparisons. Multivariate prognostic analysis was conducted using the Cox proportional hazards model. The binary logistic regression method was used to analyze the risk factors of late radiotherapy complications. Prognostic factors are shown in Table 1.

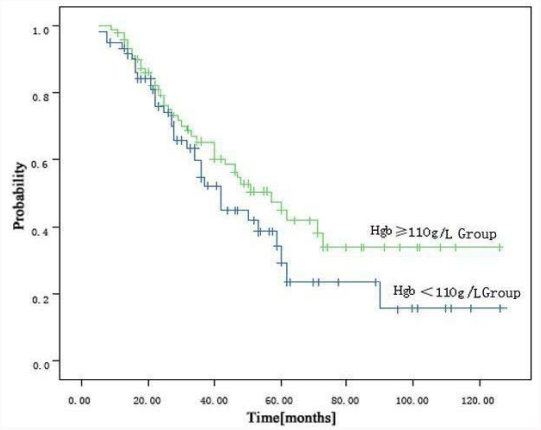

Figure 3: Survival of patients in groups Hgb <110 g/L and Hgb ≥ 110 g/L.

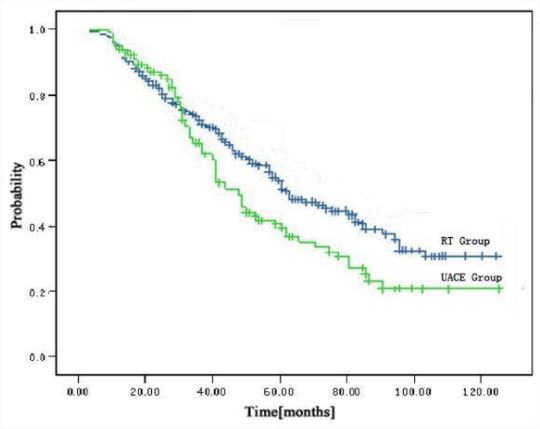

Figure 4: Effect of UACE on survival of patients with cervical cancer.

Results

Disease-specific survival (DSS)

In all patients, the average survival period was 64.2 months, and the median survival period was 60 months; the 2-year overall survival rate was 87.6%, the 5-year overall survival rate was 52.4%, and the 10-year overall survival rate was 30.2%.

The 2-year, 5-year and 10-year survival rates were 100.0%, 100.0% and 100.0%, respectively, in stage I patients, 92.4%, 67.0% and 41.2%, respectively, in stage II patients, 79.4%, 37.8% and 18.7%, respectively, in stage III patients, and 46.3%, 18.7% and 10.7%, respectively, in stage IVa patients. A comparison of survival curves of patients at different disease stages is shown in Figure 1.

Regarding age, the 2-year, 5-year and 10-year survival rates were 73.3%, 41.0% and 15.7%; 90.5%, 51.7% and 28.0%; and 87.5%, 54.2% and 36.7% for patients in <40 years group, 40 to 59 years group and ≥ 60 years group, respectively (χ^2=7.774, P=0.022). The survival curves of patients in the three age groups are shown in Figure 2.

Table 1: Factors associated with prognosis and value assignment.

Factors	Variables	Value assignment
Ages (years)	X1	<40=1, 40~59=2, ≥ 60=3
FIGO stage	X2	I=1, II=2, III=3, IVa=4
Hgb (g/L)	X31	<90=0, 90~99=1, 100~109=2, 110~119=3, ≥ 120=4
Hgb (g/L)	X32	<90=0, ≥ 90=1
Hgb (g/L)	X33	<100=0, ≥ 100=1
Hgb (g/L)	X34	<110=0, ≥ 110=1
Hgb (g/L)	X35	<120=0, ≥ 120=1
UACE	X4	UACE group=1, the other(RT group)=0
Point A radiotherapy doses (Gy)	X5	≤ 66=0, >66=1
Point B radiotherapy doses (Gy)	X6	≤ 52=0, >52=1
Irradiation interval* (Weeks)	X7	≤ 2=1, >2- ≤ 3=2, >3=3
Pathological differentiation	X8	Well=1, Moderately=2, Poorly=3
Cycles of chemotherapy	X9	≤ 1=1, 2=2, 3=3, 4=4
Survival time	t	Months
Result of follow-up	Y	Death=0, Truncation=1

Irradiation interval*: the difference between the time of the first intra cervical radiotherapy and the time of external radiotherapy.

To examine the impact of anemia on survival and prognosis of cervical cancer patients more clearly, we applied two grouping methods for analysis. (1) Five-group method: the patients were divided into five groups according to Hgb levels of <90 g/L, 90 g/L to 99 g/L, 100 g/L to 109 g/L, 110 g/L to 119 g/L and ≥ 120 g/L. The 5-year survival rates were 37.3%, 40.0%, 41.41%, 53.3%, and 61.9%, respectively, and the 10-year survival rates were 9.2%, 19.0%, 26.4%, 33.3% and 36.6%, respectively (χ^2=25.23, P=0.001). (2) Two-group method: the patients were divided into two groups according to a selected Hgb level (such as 90 g/L, 100 g/L, 110 g/L or 120 g/L), and the differences in the survival rates between the two groups were compared. The results of the two-group method are shown in Table 2. Figure 3 compared the survival curves of two groups of patients with Hgb <110 g/L and Hgb ≥ 110 g/L included in the two-group method.

The 2-year, 5-year and 10-year survival rates was 87.0%, 39.6% and 18.4%, respectively in patients who received UACE because of intractable vaginal bleeding (UACE group), and were 88.3%, 53.5% and 30.5%, respectively in the other radiotherapy-treated patients (RT group). The difference between the two groups was statistically significant (χ^2=6.840, P=0.010). The corresponding survival rate curves are shown in Figure 4.

Prognostic factors affecting survival rate

One-way ANOVA showed that the prognostic factors influencing the survival rate of cervical cancer patients included age, clinical stage, hemoglobin level, interventional therapy, total dose at location A, total dose at location B, interval between internal and external irradiation, and systemic chemotherapy. Cox multivariate regression analysis showed that the independent prognostic factors affecting the survival rate of cervical cancer were age, interventional therapy, clinical stage, hemoglobin level, systemic chemotherapy, and total dose at location A. The general clinical data and related results are shown in Table 3.

Late radiotherapy complications

In this study, severe delayed injuries to the bladder, rectum, and small intestine were evaluated according to the RTOG/EORTC criteria [1]. During the follow-up period, in all subjects, the incidence of grade II and III delayed bladder injury was 6.6%, while the incidence of grade II and III delayed small intestinal injury was 3.1%, and the incidence of grade II and III delayed rectal injury was 13.6%. No grade IV or V radiation injury was observed in this study. Backward stepwise binary logistic regression analysis showed that, within the

Table 2: Survival rates analysis of every group divided by the dichotomy method.

Group	5-year	10-year	χ^2	P
	Survival rate (%)	Survival rate (%)		
<90 g/L	37.3	9.2	0.09	0.759
≥ 90 g/L	42.3	26.1		
<100 g/L	40.0	15.2	2.62	0.105
≥ 100 g/L	45.7	29.4		
<110 g/L	40.7	19.7	3.65	0.036
≥ 110 g/L	53.7	32.1		
<120 g/L	50.0	27.4	2.64	0.104
≥ 120 g/L	61.9	36.6		

prescribed dose range of radiotherapy, age and radiotherapy dose (total doses at location A and B) were the risk factors for delayed rectal injury, while clinical stage and total dose at location B were the risk factors for delayed small intestinal injury, and interventional therapy was the only risk factor for delayed bladder injury (covariant removal criterion α=0.10). Analysis of risk factors for delayed radiotherapy injuries are shown in Table 4.

Discussion

The influence of age on the prognosis of cervical cancer patients, including those who have undergone radiotherapy or surgery, is controversial. It was reported that in elderly patients, the late stage of the disease when diagnosed and the failure to complete the treatment

Table 3: Analysis of prognostic factors affecting survival of cervical cancer.

Factors	n	DSS (%)			Median survival period	Log rank		Cox	
		2-years	5-years	10-years	(months)	χ^2	P	χ^2	P
Ages (years)						7.45	0.024	4.31	0.041
< 40	165	73.3	41.0	15.7	42				
≥ 40-<60	531	90.5	51.7	28.0	60				
≥ 60	159	87.5	54.2	36.7	62				
Clinical stage						97.9	0	48.68	0
I	26	100	100	100	92				
II	354	92.4	67.0	41.2	75				
III	370	79.4	37.8	18.7	55				
IVa	105	46.3	18.7	10.7	33				
Hgb (g/L)						3.65	0.036	11.34	0.011
< 110g/L	332	80.3	40.7	19.7	42				
≥ 110g/L	523	89.3	53.7	32.1	57				
UACE						6.23	0.02	7.8	0.01
No (RT)	723	80.5	53.5	30.5	61				
Years (UACE)	132	82.1	39.6	18.4	43				
Radiotherapy does of Point A (Gy)						5.08	0.041	4.58	0.035
≤ 66	516	83.2	44.8	21.1	54				
>66	339	78.4	55.6	33.1	61				
Radiotherapy does of Point B(Gy)						6.26	0.024	0.82	0.085
≤ 52	462	72.1	48.9	18.4	60				
>52	393	82.9	57.6	32.8	60				
Irradiation interval* (Weeks)						5.7	0.047	3.04	0.181
≤ 2	210	81.4	53.4	39.7	84				
>2- ≤ 3	426	81.0	50.8	24.2	61				
>3	219	80.6	45.2	22.9	57				
Pathological differentiation						7.29	0.113	0.54	0.263
Well (differentiated)	105	91.7	57.6	29.7	68				
Moderately (differentiated)	432	85.4	53.4	30.6	63				
Poorly (differentiated)	318	78.1	52.0	29.9	63				
Cycles of chemotherapy						10.18	0.033	7.42	0.016
≤ 1	165	77.6	42.1	13.5	45				
2	87	84.3	50.7	22.4	51				
3	185	84.3	55.0	28.1	55				
4	418	82.7	57.4	37.6	57				

Irradiation interval*: the difference between the time of the first intra cervical radiotherapy and the time of external radiotherapy.

Table 4: Correlation analysis of delayed complications of radiotherapy.

Factors	P	OR	95 % CI
Late radiation toxicity on the rectum			
Ages	0.024	1.536	1.024-1.168
Does of Point B	0.043	1.074	1.073-1.208
Does of Point A	0.031	1.108	1.010-1.764
Late radiation toxicity on the small intestine			
Stages	0.001	9.176	2.867-26.541
Does of Point B	0.009	1.695	2.194-6.108
Late radiation toxicity on the urinary bladder			
UACE	0.021	4.776	1.277-8.896

are main reasons for a poor prognosis [2]. This study showed that age is an independent prognostic factor for cervical cancer following radiotherapy treatment; for radical radiotherapy, the long-term survival rate of elderly patients is significantly higher than that of young patients. Tumor cell activity, vascular tumor thrombus rate, and pelvic lymph node metastasis rate in young patients are higher in young cervical cancer patients than in elderly patients, and high HPV infection rate and sexual activity in young patients may be among the poor prognostic factors [3].

Severe anemia indicates a later stage of the disease; therefore early diagnosis and treatment are important. Anemia is one of the prognostic factors of radiotherapy in patients with malignant tumors, mainly because of the radiation resistance of hypoxic tumor cells. Hemoglobin is the most important oxygen-carrying component in the body, and its concentration is closely related to the oxygen content in tissues and cells. Grogan et al. [4] retrospectively analyzed 605 cervical cancer patients who received radical radiotherapy in seven Canadian centers, and showed that the lowest Hgb level during radiotherapy was significantly correlated with local tumor control rate, disease-free survival rate, and overall survival rate. The results of this study showed that, the local control rate and long-term survival rate were positively correlated with Hgb level, and the long-term survival rate of cervical cancer patients could be significantly improved by increasing the Hgb level to more than 110 g/L before radiotherapy. In addition to active hemostatic therapy, the rapid and effective way to improve Hgb is to apply Erythropoietin (EPO) and inject erythrocyte suspension. Analysis of the effect of EPO on the radiotherapy of cervical cancer found that the EPO treatment group showed significantly increased long-term disease-free survival and decreased recurrence rates [5]. Although contrary conclusions have been reported previously, and blood transfusions may increase the tumor recurrence rate [6], we believe that erythrocyte suspension injection is currently the most effective way for short-term improvement of anemia.

In general, cervical cancer patients with intractable vaginal hemorrhage should be treated with uterine artery intervention before radical radiotherapy to quickly relieve cancer pain and control symptoms such as acute vaginal bleeding. In the clinical treatment of cervical cancer, uterine artery interventional surgery is usually performed as "tumor arterial infusion chemotherapy" + "super selective nutritional artery embolization" surgery. The latter can instantly devascularized the tumor tissues, resulting in tumor necrosis and a rapid reduction in size. However, this not only reduces tumor load but also leads to hypoxia of tumor cells, resulting in the radiation resistance of tumor cells and the decreased efficacy of multiple cytotoxic chemotherapeutic drugs [7], which counteracts the anti-tumor effect of UACE and reduces the long-term effect. Our previous study described the effects of Uterine Artery Infusion Chemotherapy (UAIC) and uterine artery chemoembolization before radiotherapy on the prognosis of patients: when clinical factors such as FIGO stage were comparable, UACE slightly increased the 1-year and 2-year DSS of patients with advanced cervical cancer [8]. However, with the continuation of follow-up, their 5-year and 8-year DSS decreased significantly (P=0.001). In contrast, if only UAIC was performed in uterine artery intervention before radiotherapy, the 5-year and 8-year DSS of patients in the UAIC group was significantly higher than those in the UACE group (P=0.004) and was higher than those in the general radiotherapy group (P=0.187).

Several studies have shown that pathological type and differentiation have no significant effect on the survival period of cervical cancer patients. The pathological grade of cervical squamous cell carcinoma was not significantly correlated with the 5-year survival rate, the recurrence rate, or the metastasis rate. Kobayashi et al. [9] studied the response of locally advanced cervical cancer patients to neo-adjuvant arterial infusion chemotherapy and found that squamous cell carcinoma and non-squamous cell carcinoma showed similar responses to the treatment. Considering the low sensitivity and easy recurrence of adenocarcinoma and highly differentiated squamous cell carcinoma to radiotherapy and tumor toxic drugs, the dose of radiotherapy is usually increased appropriately in clinical practice.

Concurrent chemo-radiotherapy has been proved to significantly improve the local control rate and long-term survival rate of patients with locally advanced cervical cancer. As a recommended regimen for the treatment of advanced cervical cancer, the curative effect of concurrent chemo-radiotherapy is confirmed by most researchers [10]. While eradicating micrometastasis, systemic chemotherapy can also improve the local control rate by increasing the radiosensitivity of tumor cells through the cytotoxicity of chemotherapeutic drugs. Since 1999, five large sample randomized controlled clinical trials based on cisplatin were conducted by the Gynecologic Oncology Group (GOG), the Radiation Therapy Oncology Group (RTOG), and the South West Oncology Group (SWOG), and proved that concurrent chemo-radiotherapy could significantly improve the survival rate and reduce the risk of death by 30% to 50% [11]. At present, there are two main controversial aspects in the application of systemic chemotherapy to the treatment of cervical cancer. First, for patients with stage I and stage IIa cervical cancer, whether adjuvant radiotherapy and chemotherapy should be applied together with radical surgery and radiotherapy [12]; and second, the regimen, dosage, administration route, and the optional time of chemotherapy.

The combination of external irradiation and intracervical brachytherapy differs among medical units, but it is generally believed that prophylactic dosage at the parametrium (location B) and radical dosage at the cervix (location A) should be given. Radiotherapy is the most important treatment for advanced cervical cancer, thus the prescribed dose should affect the prognosis of the patients. However, this study showed no significant difference in the survival rate between patients who received doses of ≤ 52 Gy and >52 Gy. The authors suggested that the prophylactic dosage of 46 Gy to 58 Gy at the parametrium (location B) may be more appropriate. Although the increased dosage at location A may improve the long-term prognosis of the patients, to improve the prognosis only by increasing the dose of radiotherapy is difficult in clinical practice because of the

restriction in the tolerance of normal tissues [1], and comprehensive treatment and accurate radiotherapy are better choices. Although the results of multivariate analysis in this study showed that the interval between internal and external irradiation was not a prognostic factor in cervical cancer patients, the survival rate was negatively correlated with the prolongation of the interval between internal and external irradiation. It is suggested that intracavitary brachytherapy should be applied as early as possible in radical radiotherapy for cervical cancer.

Delayed tissue radiation injury is the main reason affecting the quality of life of cervical cancer patients. The complications of radiotherapy in cervical cancer patients are mainly delayed injury to the rectum, bladder, and small intestine. In this study, the incidence of complications was similar to that reported previously [13]. The bladder bottom and triangle area are the "hot spots" of radiotherapy for cervical cancer, and the inferior bladder artery that governs this area is derived from the internal iliac artery together with the uterine artery. During uterine artery intervention, low specificity of the embolization artery vascular will lead to the inclusion of PVA particles in the inferior bladder artery, causing ectopic embolization, and then aggravating bladder injury together with radiation. This explains the anatomical basis of UACE as a strong risk factor associated with delayed bladder injury [8]. Mitchell et al. [14] suggested that the incidence of grade 2 and 3 delayed bladder injury in young patients was significantly higher than in elderly patients. In this study, age was not associated with bladder injury but it was a risk factor for delayed rectal injury.

The impact of clinical staging on the prognosis of cervical cancer is consistent in different studies, and thus is not discussed here.

Although this is a retrospective and non-random study, it also shows the general rule of prognosis for cervical cancer patients following radical radiotherapy. During the study period, new radiotherapy techniques, equipment, and anti-tumor drugs have been introduced to the clinic, thus there are still other factors affecting the prognosis of cervical cancer that need to be confirmed by further prospective data.

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