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# Analysis of Therapeutic and Adverse Effects of Cisplatin Chemotherapy and Different Dose Radiotherapy in Inoperable Esophageal Cancer

Wei LIU *, Hongyan ZHANG, Wenguang LUO, Shen QI & Peijie ZHOU

*Department of Radiation Oncology, Anhui Provincial Hospital,*
*The First Affiliated Hospital of University of Science and Technology of China, Hefei,*
*Anhui 230031, PR China*

***SUMMARY*. The aim was to compare the efficacy and toxic side effects of different doses of radiotherapy combined with cisplatin chemotherapy in the radical treatment of inoperable esophageal cancer. So, 100 patients with inoperable esophageal cancer admitted to our hospital from January 2017 to December 2017 were selected and divided into control group and research group by using envelope method. Both groups received radiotherapy combined with concurrent cisplatin chemotherapy radical therapy, the control group received high-dose radiotherapy + concurrent cisplatin chemotherapy, and the research group received low-dose + concurrent cisplatin chemotherapy. The clinical efficacy of the two groups of patients, the occurrence status of toxic adverse reactions, the level of coagulation function indicators of the two groups of patients, and the survival rate of the two groups of patients were compared. The clinical effect of the study group was better than that of the control group. The overall incidence of liver and kidney injury, bone marrow suppression, digestive tract reaction and radioactive esophagitis in the study group was lower than that in the control group ($p < 0.05$). The platelet count level in the treatment group was higher than that in the control group, and the fibrinogen and d-d levels were lower than those in the control group ($p < 0.05$). Survival rates at the 6th, 12th and 18th months in the study group were higher than those in the control group ($p < 0.05$). In the clinical treatment of patients with inoperable esophageal cancer, the use of low-dose radiotherapy combined with cisplatin chemotherapy for radical treatment has significant clinical efficacy and few toxic adverse reactions. Compared with high-dose radiotherapy, the effect on the coagulation function of patients is smaller, and the application effect is ideal, which can be considered to be widespread.**

*RESUMEN*. El objetivo fue comparar la eficacia y los efectos secundarios tóxicos de diferentes dosis de radioterapia combinada con quimioterapia con cisplatino en el tratamiento radical del cáncer de esófago inoperable. Cien pacientes con cáncer de esófago inoperable ingresados en nuestro hospital desde enero de 2017 hasta diciembre de 2017 fueron seleccionados y divididos en grupo de control y grupo de investigación. Ambos grupos recibieron radioterapia combinada con terapia radical de quimioterapia con cisplatino concurrente, el grupo de control recibió radioterapia de dosis alta + quimioterapia con cisplatino concurrente, y el grupo de investigación recibió quimioterapia con cisplatino de dosis baja + concurrente. Se comparó la eficacia clínica de los dos grupos de pacientes, el estado de aparición de reacciones adversas tóxicas, el nivel de indicadores de función de la coagulación y la tasa de supervivencia de los dos grupos de pacientes. El efecto clínico del grupo de estudio fue mejor que el del grupo de control. La incidencia global de daño hepático y renal, supresión de la médula ósea, reacción del tracto digestivo y esofagitis radiactiva en el grupo de estudio fue menor que en el grupo de control ($p <$ 0,05). El nivel de PLT en el grupo de tratamiento fue más alto que en el grupo de control, y los niveles de fibrinógeno y d-d fueron más bajos que los del grupo de control ($p < 0.05$). Las tasas de supervivencia a los 6, 12 y 18 meses en el grupo de estudio fueron más altas que las del grupo de control ($p <$ 0,05). En el tratamiento clínico de pacientes con cáncer de esófago inoperable, el uso de radioterapia de dosis baja combinada con quimioterapia con cisplatino para el tratamiento radical tiene una eficacia clínica significativa y pocas reacciones adversas tóxicas. En comparación con la radioterapia de dosis alta, el efecto sobre la función de coagulación de los pacientes es menor y el efecto de aplicación es ideal, lo que puede considerarse generalizado.

*KEY WORDS:* concurrent cisplatin chemotherapy, inoperable esophageal cancer, radiation therapy.

* Author to whom correspondence should be addressed. *E-mail:* lvfzz152@aliyun.com



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## INTRODUCTION

The incidence rate of esophageal cancer is high in China. The incidence rate is 50% and the mortality rate is the highest in the world [1]. Early middle and lower esophageal cancer can be treated surgically. However, among all the patients, more than 80% are in the middle or advanced stage of esophageal cancer, and the ideal effect of surgical treatment cannot be achieved, and the 5-year survival rate is less than 35% [2]. Therefore, comprehensive treatment has become a trend, especially for patients with advanced esophageal cancer who are not allowed surgery or are unwilling to accept surgery, the efficacy of concurrent chemoradiotherapy is superior to that of sequential therapy [3]. At the same time, we observed that there are certain differences in clinical efficacy and toxicity of different doses of radiotherapy for patients with esophageal cancer. In this study, we applied different doses of radiotherapy combined with concurrent cisplatin chemotherapy for patients with inoperable esophageal cancer, and analyzed the impact of different doses of radiotherapy on the clinical and toxic adverse reactions of patients.

## MATERIALS AND METHODS

### General data

A total of 100 patients with inoperable esophageal cancer admitted to our hospital from January 2017 to December 2017 were selected and divided into control group and study group by envelope method. There were 50 patients in the control group, including 26 male patients and 24 female patients, aged 55-76 years old, with an average age of (65.6 ± 1.2) years old. Types: 21 cases of squamous cell carcinoma, 23 cases of adenocarcinoma, and 6 cases of undifferentiated carcinoma. There were 50 patients in the study group, including 27 male patients and 23 female patients, aged 54-76 years, with an average age of (65.4 ± 1.1) years. Types: 20 cases of squamous cell carcinoma, 22 cases of adenocarcinoma, and 8 cases of undifferentiated carcinoma. The basic information of the two groups of patients is incomparable ($p > 0.05$). The patients and their family members were informed of the content of this study, and they voluntarily agreed to participate and signed the informed consent. The Ethics Committee of our hospital approved this study.

*Inclusion criteria:* 1) patients who were diagnosed as esophageal cancer and could not be treated surgically were diagnosed according to the relevant diagnostic criteria of Oncology (7th Edition) of human health 4; 2) patients without other cancers or without cancer metastasis; 3) patients without dysfunction of liver, lung, kidney, and other important organs.

*Exclusion criteria:* 1) patients with incomplete clinical data were excluded; 2) patients who dropped out of the study; 3) patients with severe dysfunction of heart, liver, lung and kidney; 4) patients with other cancers; 5) patients with rapid disease progression; 6) patients with contraindication of chemoradiotherapy.

### Treatment protocol

The patients in the control group received high-dose radiotherapy combined with concurrent cisplatin chemotherapy. After locating the visual field, according to the chest CT and barium X-ray film, the scope of radiotherapy was determined, the target area was designed, and then the radiotherapy plan was made. The primary lesions were irradiated with Siemens accelerator, once a day from week 1 to week 5. The dose is 200 cGy/time, and the total dose is 5,000-6,000 cGy. Cisplatin was administered at a dose of 20 ~ 30 mg/ (m2.d) for 3 days and pumped continuously for a total of l20 h with 5-FU400 ~ 500mg/ (m2.d) for a treatment cycle of 28 days, requiring continuous treatment for 4 cycles. In the first cycle, chemotherapy and radiotherapy were performed simultaneously, and the second cycle of chemotherapy was completed during the radiotherapy [5].

The study group received low-dose radiotherapy plus concurrent cisplatin (Manufacturer: Qilu Pharmaceutical Co., Ltd., specification: 10 mg, dosage form: injection (Sterile powder injection), batch number: National drug approval Number H37021358) treatment, and the chemotherapy method of cisplatin was the same as that of the control group. The radiotherapy dose is 150 cGy/time, and the total dose is 4,000-5,000 cGy 6. Continuous treatment was needed for 4 cycles.

### Observational index

After the course of treatment, the clinical effects of the two groups were compared, and chest X-ray film, chest CT and MRI were used to measure the status of lesion retraction. The evaluation criteria refer to the WHO evaluation criteria for the efficacy of malignant tumors: Complete response (CR): the tumor was completely

disappeared or necrotic, and the manifestation lasted for more than 4 weeks. Partial response (PR): the tumor necrosis rate reached more than 50%, the product of the two greatest diameters of the lesions decreased by more than 50%, lasting for more than 4 weeks, and no deterioration or new lesions appeared. NC (Stable disease): no significant change in tumor volume; the tumor necrosis or reduction was less than 25% or increase of tumor volume less than 25%. Progression disease: The product of the maximum two vertical diameters of the lesions increased by more than 25%. Overall response rate = CR + PR.

The toxicity and adverse reactions of the two groups were compared. The evaluation indexes included liver and kidney function damage, bone marrow suppression, gastrointestinal reaction, and radiation esophagitis. Statistical comparison was made after the treatment cycle.

The survival rates of the two groups were compared, and the patients were followed up at 6, 12, and 18 months after treatment, and the survival rates of the patients were counted.

The coagulation function indexes including fibrinogen (FIB, coagulation method), D-Dimer (D-D), platelet count (PLT) were compared between the two groups. 5 mL of fasting elbow vein blood was collected and separated by centrifugation at 3000 rpm for 10 min. D-D was measured by latex-enhanced immunoturbidimetry, while PLT was measured by electrical impedance method. The detection instrument was Domestic Pulan automatic coagulation analyzer (Model: PUN-2048-B). All the reagents and calibrators were used and operated strictly according to the instructions.

### Statistical analysis

SPSS18.0 was used to analyze the data involved in this study. $X^2$ (%) was used for counting and $t$ test ($\bar{x} \pm s$) was used for measurement. The significant difference was indicated by $p < 0.05$.

## RESULTS

Comparison of efficacy between the two groups

The clinical efficacy of the study group was better than that of the control group (p<0.05), as shown in Table 1.

### Comparison of adverse reactions between the two groups

The total incidence of liver and kidney damage, bone marrow suppression, gastrointestinal reaction and radiation esophagitis in the study group was lower than that in the control group ($p < 0.05$), as shown in Table 2.

### Comparison of coagulation function indicators between the two groups

After treatment, the PLT level of the study group was higher than that of the control group, while the FIB and D-D levels were lower than those in the control group ($p < 0.05$), as shown in Table 3.

| Groups | Cases | Complete response | Partial response | Stable disease | Progression disease | Overall response rate |
|---|---|---|---|---|---|---|
| Control group | 50 | 9 (18.0) | 13 (26.0) | 19 (38.0) | 9 (18.0) | 44.0% |
| Study group | 50 | 16 (32.0) | 18 (36.0) | 12 (24.0) | 4 (2.0) | 68.0% |
| $X^2$ | | 6.254 | 5.265 | 5.996 | 5.264 | 7.125 |
| *P* | | < 0.05 | < 0.05 | < 0.05 | < 0.05 | < 0.05 |

**Table 1**. Comparison of efficacy between the two groups (cases, %).

| Groups | Cases | Hepatic injury | Bone marrow suppression | Gastrointestinal reaction | Radiation esophagitis | Renal function impairment | Total incidence |
|---|---|---|---|---|---|---|---|
| Control group | 50 | 4 (8.0) | 3 (6.0) | 5 (10.0) | 2 (4.0) | 2 (4.0) | 32.02% |
| Study group | 50 | 2 (4.0) | 1 (2.0) | 3 (6.0) | 1 (2.0) | 1 (2.0) | 16.0% |
| $X^2$ | | 4.669 | 5.624 | 5.117 | 4.962 | 4.959 | 7.116 |
| *P* | | < 0.05 | < 0.05 | < 0.05 | < 0.05 | < 0.05 | < 0.05 |

**Table 2**. Comparison of adverse reactions between the two groups (cases, %).

| Groups | Cases | PLT (×10⁹/L) | | FIB (g/L) | | D-D (mg/L) | |
|---|---|---|---|---|---|---|---|
| | | Prior treatment | Post treatment | Prior treatment | Post treatment | Prior treatment | Post treatment |
| Control group | 50 | 208.6 ± 56.3 | 159.6 ± 35.6 | 3.1 ± 0.8 | 4.1 ± 0.7 | 0.9 ± 0.6 | 2.36 ± 1.1 |
| Study group | 50 | 207.5 ± 56.6 | 175.4 ± 26.2 | 3.1 ± 0.9 | 3.4 ± 0.8 | 0.9 ± 0.5 | 1.66 ± 0.7 |
| T value | | 1.001 | 18.625 | 1.145 | 19.326 | 1.411 | 19.635 |
| *P* value | | > 0.05 | < 0.05 | > 0.05 | < 0.05 | > 0.05 | < 0.05 |

**Table 3**. Comparison of coagulation function indexes between the two groups ($\bar{x} \pm s$).

| Groups | Cases | 6-month annual survival rate | 12-month annual survival rate | 18-month annual survival rate |
|---|---|---|---|---|
| Control group | 50 | 80.0 (40/50) | 72.0 (36/50) | 52.0 (26/50) |
| Study group | 50 | 86.0 (43/50) | 80.0 (40/50) | 64.0 (32/50) |
| $X^2$ | | 5.123 | 5.692 | 6.895 |
| *P* | | < 0.05 | < 0.05 | < 0.05 |

**Table 4**. Comparison of survival rate between the two groups (cases, %).

### Comparison of survival rate between the two groups

The survival rate at 6, 12, and 18 months in the study group was higher than that in the control group ($p < 0.05$), as shown in Table 4.

## DISCUSSION

The incidence of esophageal cancer is insidious. In the early stage of the disease, obvious symptoms will not appear, and it is difficult to diagnose in the early stage. In addition, most people do not have the habit of regular physical examination, and have been in the middle and advanced stage of cancer, especially the patients with local advanced stage. Therefore, simple surgery or treatment has not been able to play a significant role, accompanied by a reduction in the 3-year survival rate [7]. The failure of treatment of esophageal cancer is mainly due to the failure of local disease control, recurrence, and metastasis. In order to improve the survival rate of patients with advanced esophageal cancer, a lot of medical exploration has been carried out, such as preoperative radiotherapy, chemotherapy, radiotherapy and chemotherapy, postoperative radiotherapy, chemotherapy and so on [8]. Radiotherapy and chemotherapy alone can only treat local lesions, but cannot control the micrometastasis, which will hide the lesions. However, the long cycle of sequential chemotherapy will lead to the loss of opportunity. Concurrent chemoradiotherapy can not only treat the primary tumor and reduce the tumor size, but also play a therapeutic role in the hidden lesions of the body [9].

Cisplatin is commonly used in combination with chemotherapy for cancer. According to relevant information, cisplatin has the characteristics of broad-spectrum anti-cancer, strong curative effect, synergistic effect with other tumor resistance drugs, and no cross resistance. In clinical practice, cisplatin is often used in the treatment of reproductive system tumors, esophageal cancer, nasopharyngeal carcinoma, and the effect is positive [10]. There are many toxic and adverse reactions of chemoradiotherapy drugs, the main reason is that chemoradiotherapy will interfere with normal cells in the inhibition of cancer cells. The common toxic reactions include bone marrow suppression, gastrointestinal reactions, liver and kidney toxicity, and gastrointestinal reactions are serious, with the highest incidence rate, mainly including nausea and vomiting [11]. In this study, after low-dose radiotherapy, the total incidence of liver and kidney damage, bone marrow suppression, gastrointestinal reaction, radiation esophagitis in the study group was lower than that in the control group, indicating that low-dose chemoradiotherapy can reduce the toxicity and adverse reactions of patients, thus ensuring the clinical therapeutic effect. The clinical efficacy of the study

group after treatment is better than that of the control group. Previous studies have suggested that cancer cells are concentration dependent. Therefore, in order to enhance the drug concentration in the blood, high-dose radiotherapy has been used [12]. Radiation dose control is extremely important in concurrent treatment of radiotherapy and chemotherapy. Radiation liver, kidney and lung function are in direct proportion to the total radiation dose. Therefore, high-dose radiotherapy after chemotherapy will aggravate radiation liver and kidney damage, affect the prognosis of patients, and increase the death rate [13]. At present, esophageal cancer cannot be cured. Under the condition of tumor control, the main purpose of clinical treatment is to maximize the quality of life of patients. For patients with tumor, drug therapy is much better than radical treatment, which leads to bedridden and unable to take care of themselves. Therefore, low-dose radiotherapy after chemotherapy can reduce the probability of radiation-induced liver, kidney, and lung injury, and ultimately improve the quality of life of patients, at the same time, it is conducive to prolong the survival time of patients, and will not affect the curative effect.

Referring to the relevant literature, it is found that most of the patients with malignant tumor are in hypercoagulable state. Relevant research indicates that about 50% of cancer patients and 90% of patients with cancer metastasis will have abnormal coagulation function index. In the process of the occurrence and development of malignant tumor, coagulation is always accompanied by abnormal function. Tumor cells will directly or indirectly affect fibrinolysis system and blood coagulation, leading to tumor cell proliferation and metastasis [14]. Radiotherapy is a common and effective method for the treatment of malignant tumors, especially three-dimensional conformal radiotherapy plays an important role in the treatment of malignant tumors. However, radiotherapy and chemotherapy can lead to endothelial damage, make the body appear immune response, promote the release of cancer procoagulant substances, and then stimulate the coagulation system, causing coagulation dysfunction. D-D is produced by the degradation of FIB monomer. The increase of D-D level can reflect the enhancement of fibrinolytic activity and the increase of thrombin, indicating that coagulation and fibrinolysis systems are activated. The related literature shows that the D-D level in the blood of cancer patients after radiotherapy is significantly higher than that before radiotherapy. This is mainly because the necrotic cancer tissue and its products and toxins damage the adjacent tissues after radiotherapy. If the coagulation process is activated, it may aggravate the prethrombotic state, leading to disseminated intravascular coagulation and other consequences, aggravating the disease [15]. The results of this study are consistent with this conclusion. In this study, after treatment, the PLT level of the study group was higher than that of the control group, while the FIB and D-D levels were lower than those of the control group ($P < 0.05$). The reason is that the decrease of PLT in tumor patients before and after treatment is related to the suppression of bone marrow radiotherapy, and the degree of inhibition will increase and deepen with the increase of radiation dose and time. FIB belongs to glycoprotein coagulation factor, which is secreted and synthesized by liver, and has the highest content in plasma. After radiotherapy, FIB will increase in the body, which indicates that the coagulation system is activated by radiotherapy, which affects the prethrombotic state. Radiotherapy technology and radiation dose are important factors that cause radiation reaction and complications. Therefore, different radiation dose will lead to different coagulation function of tumor. The results of this study confirmed that there is a high probability of abnormal coagulation function after increasing the radiation dose. The reason for this phenomenon may be: after the radiation dose is increased, the bone marrow suppression caused by radiotherapy is aggravated, the surrounding tissues are destroyed, and the coagulation process is activated. Timely measures can effectively prevent pulmonary embolism, deep vein embolism and other complications, and improve the survival rate of patients. In this study, the survival rates of patients in the study group at 6, 12 and 18 months were higher than those in the control group ($P < 0.05$), indicating that low-dose radiotherapy has positive significance in improving the survival rate of patients.

## CONCLUSION

It can be concluded that, the clinical treatment of patients with inoperable esophageal cancer, the application of low-dose radiotherapy combined with concurrent cisplatin chemotherapy for radical treatment has significant clinical efficacy and less toxic and adverse reactions. Compared with high-dose radiotherapy, it has

less impact on coagulation function indexes of patients and has ideal application effect, which can be considered for popularization.

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