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Original Article

The clinical efficacy of extended-field radiation therapy for locally advanced cervical cancer combined with regional lymph node metastasis and its effect on the serum levels of TNF-α and S100A8

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Abstract: Objective: To evaluate the clinical efficacy of extended-field intensity-modulated radiotherapy (EF-IMRT) and remote after-loading for intracavitary radiotherapy combined with cisplatin chemotherapy (single drug) on locally advanced cervical cancer and para-aortic lymph nodes (PALN) as well as to analyze its effect on the expression levels of tumor necrosis factor alpha (TNF-α) and S100 calcium-binding protein A8 (S100A8). Methods: A total of 124 patients diagnosed with cervical cancer combined with PALN were included in this study; they were randomized into control (n=62) and observation (n=62) groups. The patients in the control group received conventional radiotherapy combined with cisplatin chemotherapy, and the patients in the observation group received EF-IMRT and remote after-loading for intracavitary radiotherapy combined with cisplatin chemotherapy. The total course of the treatment was 12 weeks, and the follow-up time was 18 months. The clinical efficacy, follow-up recurrences, and metastasis rates were evaluated after the completion of the course of the treatment. Peripheral venous blood samples were collected and the serum levels of TNF-α and S100A8 before and after the treatment were measured using ELISA. Results: The overall response rate in the observation group was significantly greater than it was in the control group, but the follow-up recurrence and metastasis rates in the observation group were significantly lower than they were in the control group ($P<0.05$ for both comparisons). The levels of TNF-α and S100A8 in both groups after the treatment were significantly greater than they were before the treatment; however, the levels in the observation group were found to be significantly lower than those in the control group ($P<0.05$). Conclusion: EF-IMRT and intracavitary brachytherapy combined with cisplatin chemotherapy are effective for patients with locally advanced cervical cancer and PALN metastasis and increase the serum levels of TNF-α and S100A8. In addition, they can increase the clinical efficacy and reduce the risk of recurrence and metastasis.

Keywords: IMRT, locally advanced cervical cancer, PALN, TNF-α, S100A8

Introduction

Cervical cancer is one of the most common malignant tumors of the female reproductive system, and we are seeing it develop at a younger age. Early surgical resection can improve the long-term survival prognosis [1]. However, 30-60% of the patients are in the middle and late stages when diagnosed. Radical simultaneous radiotherapy and chemotherapy as the main treatment has been proven to be safe and effective for patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIIB/IVA disease; some patients may further be advised to undergo surgical resection to prolong survival [2]. It was found that the major factors hindering the effect of radiotherapy and tumor recurrence are the occurrence of pelvic or para-aortic lymph node (PALN) metastases and an increase in the serum squamous cell carcinoma antigen (SCCA) [3]. The study showed that extra-pelvic lymph node metastasis is relatively common in cervical cancer with an occurrence rate of 10-30%. The percentage of PALN metastasis is the highest (8.3-9.0%) in cervical cancer, indicating the poor prognosis of the disease [4]. A previous study found that lymph node metastasis is an independent risk factor affecting clinical efficacy and survival prognosis [5]. Radio-

therapy for cervical cancer includes external beam radiotherapy and proximal radiotherapy. EFRT is primarily used for the paraventricular and lymphatic drainage areas, but brachytherapy is mainly aimed at the primary focus area. The effective combination of the two kinds of treatments can achieve a higher tumor control rate. The external beam pelvic radiotherapy is performed using the two-dimensional anterior and posterior fields or a four-field box. The advantage of this technique is that it can ensure uniform dose distribution in the tumor target area. However, the disadvantage is that the tumor and the normal tissue receive the same high dose of radiation and the radiation injury and toxic effects of the tumors adjacent to important organs has been found to increase significantly [6]. The National Comprehensive Cancer Network (NCCN) guidelines recommend that EF-IMRT based on three-dimensional images is a standard model for patients with cervical cancer treated with radical radiotherapy [7]. This kind of treatment can ensure the sufficient irradiation of the target area, a reduction in the damage to the adjacent vital organs, and the maximum coverage of the invaded PALN metastatic tissue.

Tumorigenesis and tumor metastasis are related to the activation of proto-oncogenes, the inactivation of tumor suppressor genes, and immune escape. The primary functions of the tumor necrosis factor alpha (TNF-α) are to exert a tumor killing effect, identify malignant proliferating tumor cells, and play the role of immune killing by binding to TNF-α-inducing ligands [8]. TNF-α can be highly expressed in many kinds of malignant tumors. In addition, S100A8, also known as S100 calcium-binding protein A8, belongs to the S100 family of proteins and plays an important role in tumorigenesis, antibacterial, injury repair, the inflammatory response, and immune regulation [9]. A previous study found that the stroma at the front of the tumor invasion is an important indicator of tumor malignancy, and with an increase in the density of tumor-positive cells, there is a greater probability of lymph node metastasis and vascular invasion, an increase in the TNM stage, and a decrease in the survival rate as determined by the overexpression of S100A8 [10]. At the same time, a high concentration of recombinant protein S100A8 can significantly promote the epithelial-stromal transformation, invasion, and migration of colon cancer cells in vitro, suggesting that S100A8 may mainly play the role of immune escape and increase the degree of malignance of the tumor cells. However, another study demonstrated that the expression level of S100A8 is significantly increased in malignant tumor cells [11]. Considering that the expression level of S100A8 is different in different tumors or different tumor states, its specific functions are not the same [12]. Based on the above information, the aim of this study was to further evaluate the clinical efficacy of EF-IMRT and remote after-loading for intracavitary radiotherapy combined with cisplatin chemotherapy in patients with locally advanced cervical cancer combined with regional PALN metastasis as well as to analyze its effects on the serum levels of TNF-α and S100A8. This might prove to be an important internal mechanism for effective clinical treatment.

Materials and methods

Materials

A total of 124 patients with cervical cancer combined with PALN metastasis were randomly selected for this study between January 2017 and June 2018. The inclusion criteria were as follows: 1. Diagnosed with cervical cancer (stage IIIB/IVA disease) through imaging or hysteroscopy, no primary malignant tumors of other organs, no cervical metastasis, no distant organ metastasis such as in the liver, lungs, or brain; 2. A Karnofsky score ≥70, compliance with the prescribed course of radiotherapy and chemotherapy, and without serious complications; 3. At least one evaluable tumor lesion; 4. Perfect clinical data. The exclusion criteria were: 1. Serious heart, liver, kidney, or other organ dysfunction; 2. No past medical history of cervical or pelvic surgery, radiotherapy, or chemotherapy.

All the patients were randomized into the control (n=62) and the observation (n=62) groups. The patients in the control group received conventional radiotherapy combined with cisplatin chemotherapy, and the patients in the observation group received EF-IMRT and remote afterloading for intracavitary radiotherapy combined with cisplatin chemotherapy. This study was approved by the Ethics Committee of Ankang People's Hospital.

Methods

The patients in the observation group were treated with EF-IMRT and remote after-loading for intracavitary radiotherapy combined with cisplatin chemotherapy. Extended-field radiotherapy, performed in the pelvis and the drainage area of the abdominal para-aortic lymph nodes, was used to treat the patients with cervical cancer combined with PALN. The body surface was located 1 inch above the left renal vein or the enlarged lymph nodes depending on the extent of the tumor invasion in the vagina. A 6MV/10MV-X linear accelerator was used as the radiotherapy instrument, and the number of therapies was maintained at 5 per week. Before radiotherapy, the radiotherapy range was located using a Bigbore large aperture 16-row spiral CT locator (Philips, Netherlands). The precise radiotherapy planning system (Elekta XiO, Sweden) was used (95% PTV 50.4 Gy/1.8 Gy/28F) for target delineation and dose setting.

The γ-ray remote control after-loading therapeutic machine was used in the intracavitary after-loading irradiation. The irradiation starting time was the fourth week of the external irradiation, and the irradiation dose was set at once per week with 6 Gy at the point A and a total of 5F. External irradiation was suspended on the day of intracavitary after-loading therapy. The entire radiotherapy was completed within 8 weeks.

In the synchronous single drug cisplatin chemotherapy, cisplatin for injection was obtained from the Qilu Pharmaceutical Co., Ltd., China. The drug's specification was 10 mg and the Chinese Drug Approval Number was H37021358, with the prescribed dose of 40 mm/kg for 5 times. During the treatment, the vital signs and adverse reactions of radiotherapy and chemotherapy were closely observed and the treatment was stopped if necessary. The total course of treatment was 12 weeks and the follow-up time was 18 months after the end of radiotherapy and chemotherapy.

The patients in the control group received conventional radiotherapy combined with cisplatin chemotherapy; this was according to the conventional radiotherapy regimen for cervical cancer including intracavitary after-loading radiotherapy and extracorporeal conventional field radiotherapy. The intracavitary after-loading irradiation and radiotherapy dose were the same as those used for the observation group. The whole pelvic irradiation was selected for in vitro irradiation, that is, the anterior and posterior fields were irradiated vertically. A margin of 3 cm from the upper edge of pubic symphysis was the lower boundary and an upward margin of 15 cm was the upper boundary. The midline, which extended 2 cm outwards, was the lateral boundary. Irradiation was performed five times a week at 200 cGy each time. The total amount was 5,000,000 cGy (including intracavity exposure), and the irradiation was completed within 8 weeks. The chemotherapy plan was the same as that used for the observation group.

Observation indicators

The total course of the treatment was 12 weeks. At the end of the course, the clinical efficacy, follow-up recurrences, and metastasis rates were evaluated. Peripheral venous blood was collected to quantitatively detect the serum levels of TNF-α and S100A8 before and after the treatment using an enzyme-linked immunosorbent assay (ELISA). The correlation between TNF-α and S100A8 was analyzed.

According to the pelvic CT examination, the clinical efficacy was evaluated using the solid tumor efficacy evaluation standard (RECIST) [13], which classified patients into complete remission (CR), partial remission (PR), stable disease (SD), or progressive disease (PD). CR was defined as at least 85% or greater reduction in the maximum diameter of the tumor. PR was defined as at least 50% to 84% reduction in the maximum diameter of the tumor. SD was defined as a reduction of the maximum diameter of tumor by <49%. PD was defined as no significant reduction or a continuous increase in the maximum diameter of tumor. Total efficiency response rate (RR) = (CR + PR)/total number of cases × 100%.

In the anticoagulant tube, 6 mL of morning fasting elbow venous blood was collected. After 2500 r/min centrifugation for 15 min, the upper serum was taken and stored at -80°C. TNF-α and S100A8 kits were purchased from the Sigma Company, USA, and the assay was conducted according to the manufacturer's protocols.

Table 1. Comparison of the baseline data of the two groups

Group	Control group (n=62)	Observation group (n=62)	t/χ^2	P
Age (year)	64.2±6.5	63.9±6.3	0.563	0.521
BMI (kg/m^2)	22.3±1.7	22.5±1.6	0.263	0.729
Tumor stage			0.328	0.955
IIB	18	19		
IIIA	16	14		
IIIB	21	23		
IVA	7	6		
Maximum tumor diameter (cm)	4.9±1.6	4.7±1.5	0.421	0.569
PALN (n)	1.6±0.5	1.5±0.4	0.196	0.823
SCCA (μg/L)	13.5±3.2	13.9±3.5	0.632	0.359

Note: BMI: body mass index; PALN: para-aortic lymph node; SCCA: serum squamous cell carcinoma antigen.

Table 2. Comparison of the clinical efficacy in the two groups (n (%))

Group	N	CR	PR	SD	PD	RR
Control group (n=62)	62	19 (30.6)	16 (25.8)	18 (29.0)	9 (14.6)	35 (56.4)
Observation group (n=62)	62	26 (41.9)	20 (32.3)	11 (17.7)	5 (8.1)	46 (74.2)
χ^2						4.308
P						0.038

Note: CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; RR: response rate.

Table 3. Comparison of the recurrence and metastasis rates in the two groups (n (%))

Group	N	Recurrence	Metastasis	Total incidence
Control group (n=62)	62	9 (14.6)	3 (4.8)	12 (19.4)
Observation group (n=62)	62	3 (4.8)	1 (1.7)	4 (6.5)
χ^2				4.593
P				0.032

Statistical analysis

SPSS 20.0 statistical software was used for the data analysis. The data obtained from the two groups were compared using t-tests and expressed as χ^2 tests. P<0.05 was considered a statistically significant difference.

Results

Comparison of the baseline data of the two groups (P>0.05) (**Table 1**).

Comparison of clinical efficacy in the two groups

The total course of treatment was 12 weeks. After the end of the treatment, the total effective rate in the observation group was found to be significantly greater than the total effective rate in the control group (P< 0.05) (**Table 2**).

Comparison of the recurrence and metastasis rates in the two groups

The recurrence and metastasis rates in the observation group were significantly lower than they were in the control group (P<0.05) (**Table 3**).

Comparison of the serum levels of TNF-α in the two groups before and after the treatment

The serum levels of TNF-α in both groups after the treatment were significantly greater than they were before the treatment. However, the levels in the observation group were significantly lower than the levels in the control group; this difference was statistically significant (P<0.05) (**Table 4**).

Comparison of the serum levels of S100A8 in the two groups before and after the treatment

The serum levels of S100A8 in both groups after the treatment were significantly greater than they were before the treatment. However,

Table 4. Comparison of the TNF-α serum levels in the two groups before and after the treatment (mmol/L)

Group	N	Before treatment	After treatment	t	P
Control group (n=62)	62	125.6±42.3	176.8±54.5	25.639	<0.001
Observation group (n=62)	62	121.9±56.8	146.9±53.2	14.562	<0.001
t		0.296	19.689		
P		0.822	<0.001		

Note: TNF-α: tumor necrosis factor alpha.

Table 5. Comparison of the S100A8 serum levels in the two groups before and after the treatment (mmol/L)

Group	N	Before treatment	After treatment	t	P
Control group (n=62)	62	65.9±15.8	95.8±19.6	15.251	<0.001
Observation group (n=62)	62	64.3±16.6	82.5±14.7	10.448	<0.001
t		0.285	13.265		
P		0.863	<0.001		

Note: S100A8: S100 calcium-binding protein A8.

the levels in the observation group were significantly lower than they were in the control group (P<0.05) (**Table 5**).

Discussion

In a previous study, 298 patients with stage IB1/IIB cervical cancer underwent PALN resection [14]. We found that the rate of PALN metastasis was 8.7%. Common iliac lymph node metastasis (P<0.001) and the positive number of pelvic lymph nodes (P<0.001) were independent risk factors for PALN metastasis. Modulated radiotherapy significantly reduced the tumor load, tumor diameter, molecular structure of tumor production of inhibitory antigen and immune escape as well as block the lymphatic pathway and improve the effect of chemotherapy for patients with locally advanced cervical cancer; it also increased the probability of surgical resection [15, 16].

In this study, a prospective randomized controlled trial was used to analyze the effect and follow-up prognosis of EF-IMRT and intracavitary after-loading irradiation combined with cisplatin chemotherapy in patients with cervical cancer with PALN metastasis. Our observations suggest that the total effective rate in the observation group was significantly greater than it was in the control group. The complete remission and partial remission rate in the observation group was 74.2%. In addition, it was confirmed that simultaneous radiotherapy and chemotherapy is an effective strategy. The precise radiotherapy scheme for cervical cancer included three steps: imaging the accurate localization, planning the design, and the actual irradiation. Based on the CT localization and accurate radiotherapy planning system, IMRT technology was used for determining the accurate definition of the target area, clarifying the changes in the target area and the coping, and seeing the placement and quality control of the organ movement in the treatment, thereby improving the accurate irradiation dose for the target tumor [17]. Clinical target volume (CTV) includes the gross tumor volume (GTV) and the microscopic subclinical tumors. CTV in radical radiotherapy includes the cervix, the uterine body, the periuterine area, the partial vagina, and the lymph node drainage area [18]. IMRT can increase the target dose to 65 Gy, which is advantageous in protecting the small intestine, rectum, bladder, and other organs. Using this technique, the ideal dose distribution can be determined, the adjacent endangered organs can be protected, the clinical effect is satisfactory, the toxicity and side effects can be reduced, the effective rate can be improved, and the survival can be prolonged [19]. After 18 months of follow-up, the recurrence and metastasis rates in the observation group were lower than they were in the control group, suggesting that the long-term prognosis of cervical cancer with lymph node metastasis treated using the IMRT technique is better.

Further detection showed that the serum levels of TNF-α and S100A8 in both the groups after the treatment were significantly greater than they were before the treatment; it is to be noted that the levels in the observation group were significantly lower than those in the control group. The difference was statistically significant. SX Han et al. pointed out that TNF-α-mediated apoptosis gene single nucleotide site (SNP) mutation is closely related to the occurrence of cervical cancer [20]. TNF-α is mainly expressed in activated T lymphocytes and macrophages, and its main function is to inhibit tumorigenesis and resist viral infection [21]. TNF-α can further recruit pro-inflammatory cytokines such as IL-6, activate the NF-κB signal pathway, and initiate the process of tumor apoptosis [22]. As important proto-oncogenes, the expression levels of TNF-α, tumor protein p53 (p53), and the fas cell surface death receptor (FAS) in the serum of patients with cervical cancer were found to be significantly higher than those observed in the healthy controls; the levels were closely related to tumor stage, histological differentiation, invasion, and lymph node metastasis [23]. It is thought that the up-regulation of the expression level of TNF-α might be more beneficial to the malignant proliferation, invasion, and metastasis of tumor cells. TNF-α may play a positive role in the early proliferation and lymph node metastasis of the tumor.

S100A8 is produced by granulocytes, monocytes, and epithelial cells and can promote inflammation, feedback regulation, and activate fingerprint reprogramming [24]. In addition, S100A8 is regulated by a variety of inflammatory factors. P38 mitogen-activated protein kinase (p38-MAPK), c-Jun amino-terminal kinase (JNK), NF-κB, and other signaling pathways affect the proliferation and invasion abilities [25]. Q Liu et al. pointed out that S100A8 is highly expressed in cervical squamous cell carcinoma [26]. Intracellular S100A8 protein, as a calcium sensor, can activate NADPH oxidase, increase the activity of reactive oxygen species and NF-κB, and stimulate the expression of TNF-α and IL-8 [27]. As an extracellular ligand, the extracellular S100A8 protein mainly plays the role of cytokine and chemokine, enhances cascade reaction, and promotes the inflammatory response and tumor immune escape [28]. Therefore, some researchers believe that S100A8 can inhibit the ability of cell invasion and migration. However, some studies have shown that the expression of S100A8 is increased in a variety of tumors providing a favorable microenvironment for tumor cell proliferation and metastasis [29]. The up-regulation of TNF-α and S100A8 expression might promote tumor early proliferation and lymph node metastasis.

In conclusion, EF-IMRT and intracavitary afterloading irradiation combined with cisplatin chemotherapy is effective in patients with locally advanced cervical cancer with PALN metastasis, and it increases the levels of TNF-α and S100A8, which are related to clinical efficacy, recurrence, and metastasis. However, due to different tumor types and different tumor states, the expressions of TNF-α and S100A8 are different, and their specific functions are not similar. The local microenvironment in vivo and in vitro also has an important effect on the expressions and functional realizations of TNF-α and S100A8. Therefore, further pertinent research and analysis is needed.

Disclosure of conflict of interest

None.

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