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ORIGINAL ARTICLE

Preoperative neoadjuvant chemotherapy combined with radical surgery in cervical cancer

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Summary

Purpose: *To investigate the efficacy of preoperative neoadjuvant chemotherapy combined with radical surgery on cervical cancer patients and its effect on the prognosis of patients and serum squamous cell carcinoma antigen (SCC-Ag) level.*

Methods: *163 patients with cervical cancer composed the research group. Among them, 72 patients treated with radical resection of cervical cancer were enrolled in the control group, while the remaining 91 patients were enrolled in the study group and treated with preoperative neoadjuvant chemotherapy combined with radical resection of cervical cancer. The clinical indicators during and after the surgery, as well as the efficacy, were compared between the two groups. Serum SCC-Ag level before and after the treatment was measured by enzyme-linked immunosorbent assay (ELISA).*

Results: *The total effective rate of the study group was statistically higher than that of the control group ($p<0.05$). Seven cases (9.72%) of adverse reactions occurred in the control group. Thirteen cases (12.09%) of adverse reactions occurred in the study group. The serum SCC-Ag levels of the two groups after the treatment were significantly lower than those before the treatment, with a sharper decrease in the study group ($p<0.05$).*

Conclusion: *Preoperative neoadjuvant chemotherapy combined with radical surgery has remarkable efficacy in cervical cancer patients, and can significantly reduce serum SCC-Ag levels in patients, which is worthy of clinical promotion.*

Key words: *cervical cancer, preoperative neoadjuvant chemotherapy, prognosis, radical surgery, serum SCC-Ag*

Introduction

Cervical cancer is a common malignant tumor in women [1], with high mortality worldwide [2]. Recent years have seen an increase in the incidence and mortality of cervical cancer in young women under 30 years old [3]. Currently, surgery is the dominant clinical treatment for cervical cancer, often combined with chemotherapy, radiotherapy, immunotherapy, etc. [4]. Surgery can give the best control of disease progression and reduce the local disease recurrence [5]. However, the traditional radical surgery will cause severe damage to the physiological function of the ovaries and impair the reproductive function of patients to some extent [6]. Treating cervical cancer with radical surgery alone usually leads to high recurrence rate and greatly affects the patient quality of life [7]. The

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mechanism of chemotherapy is to prevent the proliferation, infiltration and metastasis of cancer cells [8]. Clinically, postoperative chemotherapy is often adopted to eliminate microscopic cancer lesions remaining after surgery and improve the efficacy of surgery [9]. Whether preoperative neoadjuvant chemotherapy combined with radical surgery can significantly improve the efficacy of traditional radical treatment and the survival of patients is very worthy of exploration.

Cisplatin, one of the most widely used chemotherapeutic agents in oncology [10], which is commonly used in the treatment of reproductive system tumors, is one of the most typical drugs in combination chemotherapy. Paclitaxel is a taxane with anticancer activity [11], which has good efficacy in ovarian cancer when combined with cisplatin. Therefore, paclitaxel and cisplatin were selected as drugs of the preoperative neoadjuvant chemotherapy in this study. Squamous cell carcinoma antigen (SCC-Ag) is the prominent cancer marker for cervical squamous cell carcinoma [12], making it practical to monitor the efficacy, recurrence, metastasis, and prognosis of disease.

This study explored the efficacy of preoperative neoadjuvant chemotherapy (paclitaxel plus cisplatin) combined with radical surgery for patients with cervical cancer and its effect on serum SCC-Ag level and prognosis.

Methods

General information

163 patients with cervical cancer admitted to the People's Hospital of Zhangqiu Area from September 2013 to July 2015 comprised the research subjects. Among them, 72 patients were enrolled in the control group and treated with radical resection of cervical cancer, while the remaining 91 patients were enrolled in the study group and treated with preoperative neoadjuvant chemotherapy combined with radical resection of cervical cancer. This trial obtained the approval by the ethics committee of the People's Hospital of Zhangqiu Area and signed informed consent was provided from all subjects.

Inclusion and exclusion criteria

Inclusion criteria: patients diagnosed with cervical cancer; patients treated in the People's Hospital of Zhangqiu Area; patients aged from 18 to 70 years; patients showing cooperation with the therapeutic team; patients who themselves or whose immediate family members signed the informed consent forms; patients with a complete medical record. Exclusion criteria: patients with severe dyfunction of important organs such as heart, liver, spleen, lung, kidney; patients with mental illness, speech and language impairment; pregnant or lactating patients; patients with surgical contraindications; patients with drug allergy.

Surgical methods

In the control group, each patient was intubated and given general anesthesia. A longitudinal incision of 18 to 29 cm in length was cut in the middle of the left side of the pubic symphysis with the patient placed in supine position. After opening the abdomen and checking that the liver and gallbladder and other organs were devoid of metastases, an incision was made in the vaginal wall by circumcision, and the uterus was taken out before performing lymph node dissection.

In the study group, patients received neoadjuvant chemotherapy before surgery: liposomal paclitaxel for injection was intravenously injected at a dose of 135 mg/m^2 (Nanjing Lvye Pharmaceutical Co., Ltd., China Food and Drug Administration Approval No. H20030357), cisplatin injection was intravenously injected at a dose of 100 mg/m^2 (Qilu Pharmaceutical Co., Ltd., China Food and Drug Administration Approval No. H37021358). The second chemotherapy cycle followed after three weeks of the first chemotherapy. After 2 to 3 cycles of chemotherapy, patients who met the surgical conditions were radically operated for cervical cancer, as performed in the control group.

Outcome measures Comparison of clinical efficacy between the two groups Efficacy evaluation criteria

The evaluation was carried out in accordance with the WHO Tumor Response Criteria. Complete response (CR): complete disappearance of all tumor lesions which was confirmed for at least 4 weeks. Partial response (PR): at least a 50% decrease in tumor lesion diameters which was confirmed for at least 4 weeks. Stable disease (SD): no greater than a 25% decrease or no greater than a 20%

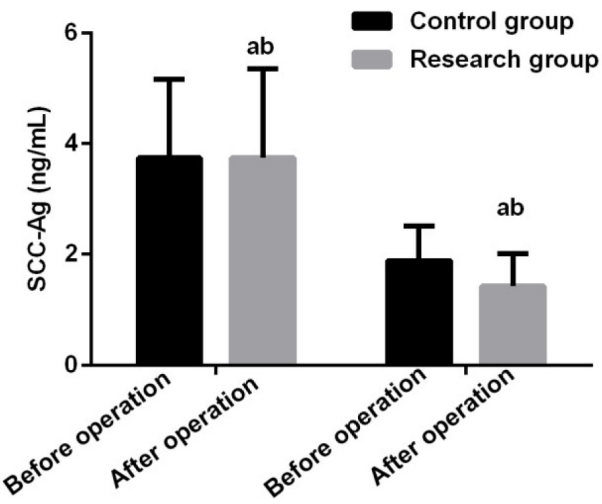

Figure 1. Comparison of serum SCC-Ag levels before and after the operation in the two groups. The serum levels of SCC-Ag in the two groups after the operation were statistically lower than those before the operation ($p<0.05$). No statistical difference was detected between the two groups before the operation in serum SCC-Ag levels ($p>0.05$). The level of SCC-Ag in the study group was significantly lower than that in the control group after the operation ($p<0.05$). a indicates comparison with the control group, and b indicates comparison with the data before the operation ($p<0.05$).

increase in tumor lesion diameters. Progressive disease (PD): at least a 25% increase in tumor lesion diameters or new lesions. Number of total response (TR) = $CR_5 + PR_5$.

Comparison of clinical indicators between the two groups during the operation

The heart rate, systolic and diastolic blood pressure, operation time, blood transfusion during the operation, blood loss during the operation, and the number of dissected lymph nodes were recorded and compared between the two groups.

Comparison of clinical indicators between the two groups after the operation

The flatus time after the operation, defecation time after the operation, duration of urethral indwelling, use of analgesic drugs, and adverse reactions were recorded.

Comparison of serum SCC-Ag levels before and after the operation in the two groups

Blood samples were collected before and after the operation in both groups. The serum level of SCC-Ag was detected by enzyme-linked immunosorbent assay (ELISA) (Beijing Baiaolaibo Technology Co. Ltd., ABS11915), in strict accordance with the kit instructions.

Prognosis and survival

A 3-year follow-up was conducted via telephone, correspondence, etc.

Statistics

Statistical calculations were conducted by SPSS24.0 statistical software (Shanghai Yuchuang Network Technology Co., Ltd.). All the graphs were drawn using Graphpad8 software (SOFTHEAD Inc.). The results were checked twice. The count data were expressed as rates and compared between groups by the chi-square test. The measurement data were expressed as mean±standard deviation and compared between groups by the independent t-test. The survival curves of both groups were made using the Kaplan-Meier method and compared by the Log-rank test. A statistical difference was recognized if $p<0.050$.

Results

Comparison of serum SCC-Ag levels before and after the operation in the two groups

The serum levels of SCC-Ag in the two groups after the operation were statistically lower than those before the operation ($p<0.05$). No statistical difference was detected between the two groups before the operation in serum SCC-Ag levels ($p>0.05$). After the operation, the SCC-Ag level of the study group was 1.43±0.59 ng/ml, statistically lower than that of the control group (SCC-Ag) which was 1.89±0.63 ng/mL ($p<0.05$; Figure 1).

Table 1. Comparison of clinical data

	Control group (n=72)	*Study group (n=91)*	*x^2 or t*	*p value*
Age (years)	49.42±9.61	48.77±10.2	0.412	0.680
BMI (kg/m^2)	20.86±2.14	20.41±1.73	1.485	0.139
Duration of disease (weeks)	5.24±1.54	5.22±1.36	0.087	0.930
Tumor size, cm, n (%)			<0.001	0.991
< 4	49 (68.06)	62 (68.13)		
≥ 4	23 (31.94)	29 (31.87)		
FIGO stage, n (%)			0.448	0.502
Stage I-IIa	43 (59.72)	59 (64.84)		
>Stage IIb	29 (40.28)	32 (35.16)		
Lymph node metastasis, n (%)			0.096	0.756
Yes	19 (26.39)	26 (28.57)		
No	53 (73.61)	65 (71.43)		
Smoking, n (%)			0.077	0.781
Yes	13 (18.06)	18 (19.78)		
No	59 (82.94)	73 (80.22)		
Drinking alcohol, n (%)			0.014	0.903
Yes	18 (25.00)	22 (24.18)		
No	54 (75.00)	69 (75.82)		
Exercise habits, n (%)			0.027	0.869
Yes	46 (63.89)	57 (62.64)		
No	26 (36.11)	34 (37.36)		

Prognosis and survival curve

The two groups of patients were followed up for 3 years by telephone, reexamination and correspondence, etc., with a success rate of 86.23%. The 3-year survival rate in the control group was 75.00% (54/72), while the 3-year survival rate in the study group was 79.12%. (72/91), and the difference in the 3-year survival rate between the two groups was not statistically significant (p>0.05; Figure 2).

General information

The two groups of patients were comparable because of lack of statistical difference in age, BMI, duration of disease, tumor size, FIGO stage, lymph node metastasis, smoking, drinking, and exercise habits (p>0.05; Table 1).

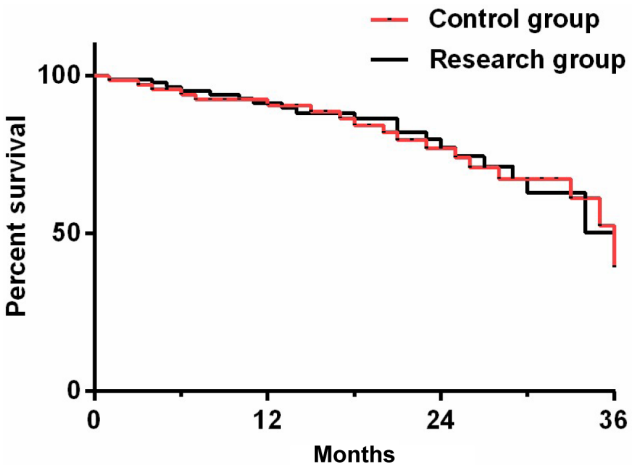

Figure 2. Survival curves of the two groups of patients. The 3-year survival rate in the control group was 75.00% (54/72), while the 3year survival rate in the study group was 79.12% (72/91), and the difference in the 3year survival rate between the two groups was not statistically significant (p>0.05).

Comparison of clinical efficacy between the two groups

In the control group, the treatment outcome was total response in 58 patients, SD in 11, and PD in 3. In the study group, the treatment outcome was total response in 83 patients, SD in 6, and PD in 2. A statistical difference was recognized between the two groups in the number of total response (p<0.05; Table 2).

Comparison of clinical indicators between the two groups during the operation

All the patients in the two groups completed the operation without intraoperative death. The two groups were not statistically different in heart rate, systolic and diastolic blood pressure (mmHg), blood loss during the operation (ml), and blood transfusion during the operation (ml) (p>0.05). The number of dissected lymph nodes in the study group was statistically lower than that of the control group (p<0.05; Table 3).

Comparison of clinical indicators and adverse reactions between the two groups after the operation

The two groups were not statistically different in flatus time after the operation (d), defecation time after the operation (d), and duration of urethral indwelling (d) (p>0.05). The number of patients using analgesic drugs after the operation in the study group was higher than that in the con-

Table 2. Comparison of clinical efficacy between the two groups

Clinical efficacy	*Control group (n=72)*	*Study group (n=91)*	x^2	*p value*
CR	35	58		
PR	23	25		
SD	11	6		
PD	3	2		
Total response	58	83	4.708	0.048

Table 3. Comparison of clinical indicators between the two groups during the operation

Clinical indicator	*Control group (n=72)*	*Study group (n=91)*	*t*	*p value*
Heart rate	75.63±7.23	76.31±6.39	0.636	0.525
Systolic blood pressure (mmHg)	138.52±8.39	137.29±8.27	0.937	0.350
Diastolic blood pressure (mmHg)	79.38±7.85	80.45±6.94	0.922	0.357
Operation time (min)	259.26±19.39	238.39±21.52	6.421	< 0.001
Blood loss during the operation (ml)	355.42±24.58	357.16±21.38	0.482	0.629
Blood transfusion during the operation (ml)	373.19±18.36	369.25±20.37	1.280	0.202
Number of lymph node dissection	17.21±4.23	13.37±3.85	6.053	< 0.001

Table 4. Comparison of clinical indicators between the two groups after the operation

Clinical indicators	*Control group (n=72)*	*Study group (n=91)*	x^2 *or t*	*p value*
Flatus time after the operation (d)	1.48±0.51	1.52±0.39	0.567	0.571
Defecation time after the operation (d)	2.14±0.72	2.18±0.81	0.328	0.742
Duration of urethral indwelling (d)	8.28±1.33	8.29±1.42	0.046	0.963
Number of patients using analgesic drugs (case)	62	78	0.005	0.924

Table 5. Comparison of adverse reactions between the two groups after the operation

	Control group (n=72)	*Study group (n=91)*	x^2	*p value*
Infection	2	1		
Lymphocyst	1	2		
Urinary retention	1	2		
Venous thrombosis	2	1		
Allergy	1	3		
Myelosuppression	0	2		
Complication (case)	7	11	0.229	0.632

trol group, but the difference was not statistically significant (p>0.05; Table 4).

Seven cases of adverse reactions were observed in the control group, with an incidence rate of 9.72%: 2 with infection, 2 with venous thrombosis, 1 with lymphocyst, 1 with urinary retention and 1 with allergy. Eleven cases of adverse reactions were observed in the study group, with an incidence rate of 12.09%: 1 with infection, 1 with venous thrombosis, 2 with lymphocyst, 2 with urinary retention, 2 with myelosuppression and 3 with allergy (Table 5).

Discussion

Cervical cancer is a common malignant tumor of the female reproductive system [13]. The pathogenesis of cervical cancer remains unclear, but it has been confirmed that women with early marriage, early childbirth, prolificacy and disorganized sexual life have a higher prevalence, and that human papillomavirus (HPV) is closely related with cervical cancer [14,15]. Surgery and radiation therapy are the dominant treatment methods for cervical cancer [16]. The treatments for locally advanced and metastatic disease include radiotherapy and chemotherapy [17]. Preoperative neoadjuvant chemotherapy combined with radical surgery is clinically practicable. Danilovic et al adopted sorafenib as preoperative treatment to reduce the tumor size and create surgical conditions for a patient with inoperable papillary thyroid cancer [18]. Mahmoud et al. demonstrated in their study that neoadjuvant chemotherapy can improve the quality of life of patients with cervical cancer [19]. This study explored the efficacy of preoperative neoadjuvant chemotherapy combined with radical surgery in cervical cancer patients and its effect on the prognosis of patients and serum SCC-Ag level, hoping to provide a clinical basis for the treatment of cervical cancer.

According to the results, the treatment outcome was total response (CR 5+PR 5) in 58 patients in the control group and in 83 patients in the study group, which suggested that preoperative chemotherapy can significantly improve the therapeutic effect and quality of life of patients by significantly reducing the size of tumor lesions. The operation time and the number of dissected lymph nodes in the study group were statistically lower than those in the control group, suggesting that preoperative neoadjuvant chemotherapy can favor the treatment of cervical cancer, narrow the tumor lesions, and significantly reduce the number of lymph nodes in patients. Such results are consistent with the study made by Mechera R et al who studied the number of lymph nodes in patients with rectal cancer after rectal resection combined with neoadjuvant radiotherapy [20]. The incidence of adverse reactions in the study group was statistically higher than in the control group. The adverse reactions in the study group were mostly caused by chemotherapy. Paclitaxel, a cytotoxic antineoplastic agent which is extracted from the bark of yew tree, is commonly used in the first- and second-line treatment of ovarian cancer, breast cancer and non-small cell lung cancer [21]. Its common adverse reactions are allergies [22]. Cisplatin mainly achieves its anti-tumor effect by inhibiting DNA replication [23]. Its inhibition on the human hematopoietic system [24] usually occurs after around 3

weeks of chemotherapy. Scandurra et al found that the combination of paclitaxel-ifosfamide-cisplatin (TIP chemotherapy), was highly efficient in treating advanced or recurrent cervical cancer with low toxicity [25]. SCC-Ag belongs to glycoproteins, which are mainly involved in tumor infiltration and metastasis. The SCC-Ag level is a reflection of tumor size [26]. The serum level of SCC-Ag in the study group was lower compared with the control group ($p<0.05$). It is suggested that preoperative neoadjuvant chemotherapy combined with radical surgery can reduce and even eliminate micrometastases. The SCC-Ag levels in this study was consistent with the change of SCC-Ag levels in the study of paclitaxel combined with cisplatin in treating advanced esophageal cancer conducted by Hu et al [27]. No statistical difference was detected in the 3-year survival rate between the two groups, suggesting that the reduction in the lymph node number after preoperative neoadjuvant chemotherapy combined with radical surgery does not lead to a reduction in the survival rate.

This study observed the differences in the postoperative adverse reactions between the study group and the control group. However, such findings are subject to limitations because of the short follow-up time and the lack of analysis of the tumor recurrence. In future studies, the follow-up should be extended to explore the factors affecting the quality of life of patients after surgery, so as to further verify the results of this study.

In summary, on the one hand, the application of preoperative neoadjuvant chemotherapy in patients with cervical cancer can significantly improve the treatment efficacy and reduce metastasis to the lymph nodes, while on the other hand, it can increase the incidence of adverse reactions, impact the patient quality of life and create worries about complications.

Conflict of interests

The authors declare no conflict of interests.

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