Prognostic Analysis of Local Advanced Cervical Cancer After Neoadjuvant Chemotherapy

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Abstract: Background: This study aims to analyze the factors influencing the survival and prognosis of patients with locally advanced cervical cancer (LACC) after neoadjuvant chemotherapy (NACT), so as to provide theoretical guidance for clinical work. Methods: A total of 263 patients diagnosed with stage IB3, IIA2, IIB and IIIC1r cervical cancer according to FIGO 2018 criteria were enrolled in this retrospective study. They were admitted to First Affiliated Hospital of Chongqing Medical University from January 2018 to December 2021. After receiving 1-4 cycles of "platinum + paclitaxel" chemotherapy and effective NACT, the patients accepted surgery including radical hysterectomy and pelvic lymph node dissection. All patients with one of high-risk factors or two of medium-risk factors are exposed to additional radiation according to post-operative pathological risk factors. Patients were divided into two parts based on whether or not radiotherapy was supplemented after surgery. The baseline characteristics, treatment plan, pathological characteristics and survival prognosis of the two groups were compared in this study. The main endpoint of the study was recurrence or death within 2 years. The 2-year progression-free survival (PFS) rate was compared between the two groups in order to analyze the risk factors affecting prognosis. Results: In this study, 59 patients without supplemental radiotherapy and 204 patients with supplemental radiotherapy were included. The 2-year PFS rate was 98.10% and 98.90% respectively (p=0.606) in the group with and without supplementary radiotherapy. Univariate analysis showed that parastatal infiltration and lympho-vascular space infiltration were risk factors for 2-year PFS, while multivariate analysis showed that only lympho-vascular space infiltration was independent risk factor for PFS. Conclusion: In conclusion, NACT can also reduce the occurrence of radiotherapy in addition to obtaining the opportunity of surgery, so as to improve the quality of life of patients without affecting survival. Meanwhile, LVSI is an independent risk factor for progression-free survival in patients with locally advanced cervical cancer who receive NACT. For such patients, complementary treatment after surgery is more helpful to ensure prognosis.

Keywords: Cervical Squamous Cell Carcinoma; Neoadjuvant Chemotherapy; Radical Surgery

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1 Introduction

Cervical cancer is one of the diseases affecting women's health worldwide [1]. Cervical cancer is reported to be the fourth most common and the fourth leading cause of malignancy-related death in women globally [2]. In China, the incidence of cervical cancer ranks second only to breast cancer. For developing countries, due to inadequate vaccination and screening, many cervical cancer patients have been diagnosed with LACC at the first time, and concurrent chemoradiotherapy (CCRT) has been recognized as the standard treatment for most locally advanced cervical cancer. However, locally advanced cervical cancer occurs mostly in developing countries or

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regions, and the shortage of radiotherapy equipment and the cost of treatment limit the standard treatment of cervical cancer, so NACT is always used as an alternative treatment.

Therefore, in this study, for patients with cervical squamous cell carcinoma who received effective NACT combined with radical surgery (RS) in our hospital in the past 3 years, the medical records of the patients were retrospectively analyzed, the clinical prognosis of the patients was compared, and the risk factors affecting the prognosis were analyzed, in order to provide reference for clinical work.

2 Methods

2.1 Study Design and Participants

From January 2018 to December 2021, 863 cervical cancer patients receiving NACT were treated in the First Affiliated Hospital of Chongqing Medical University, as shown in Figure 1. After inclusion and exclusion criteria, the staging was corrected according to the new staging of FIGO 2018. The clinical data of 263 patients with stage IB3, IIA2, IIB and IIIC1r cervical squamous cell carcinoma were retrospectively collected.

Patients were eligible if they were cervical squamous cell carcinoma with stage IB3, IIA2, IIB or IIIC1r; and received "paclitaxel + platinum-based" chemotherapy regimen before radical surgery; and had ECOG score ≤1; and had complete clinical data. Patients were excluded from this study if they had 1) other malignant tumors; 2) distant metastasis; 3) histological types other than squamous cell carcinoma; 4) radiotherapy before surgery; 5) anaphylaxis or serious side effects to chemotherapy; 6) poor efficacy for chemotherapy (Figure 1).

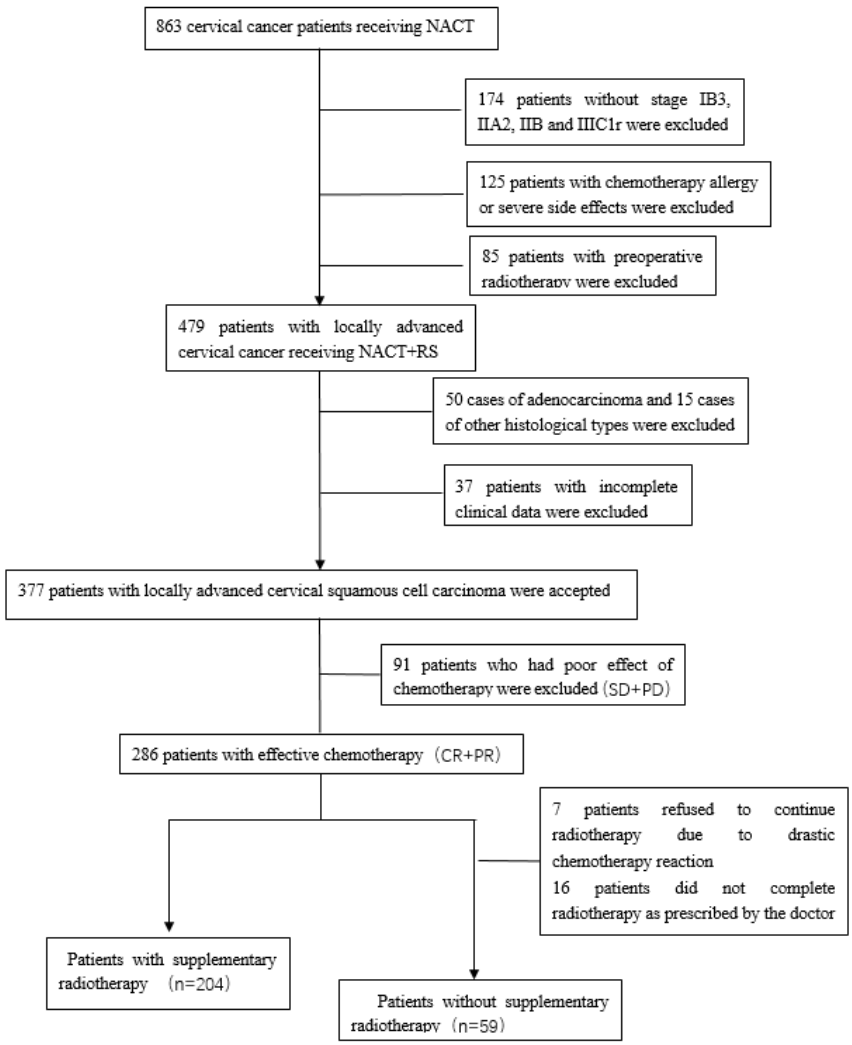

Figure 1 The flow chart of group

This trial was conducted in accordance with applicable regulatory requirements and the principles of the Declaration of Helsinki. All patients provided signed informed consent prior to participating.

According to postoperative adjuvant therapy, patients were classified into two groups—with radiotherapy and without radiotherapy.

2.2 Therapeutic Plan

All patients received "platinum + paclitaxel" chemotherapy regimen with doses of paclitaxel 135-175 mg/m^2, docetaxel 70-75 mg/m^2, cisplatin 75-80 mg/m^2, Nedaplatin 80-100 mg/m^2. Carboplatin dose was calculated according to area under blood concentration-time curve =5. Every 3 weeks was a chemotherapy cycle. Before each course of chemotherapy, physical examination was conducted by clinicians to determine the degree of focal shrinkage, and relevant auxiliary examinations (blood routine, liver and kidney function, SCC, et al) were performed to evaluate the chemotherapy effect. Radical hysterectomy and pelvic lymph node dissection were performed 3-4 weeks after the last chemotherapy for patients with effective chemotherapy, and radiotherapy was recommended for patients with ineffective chemotherapy.

For patients with stage I and IIA cervical squamous cell carcinoma, the ovarian metastasis rate is less than 1% [3]. Therefore, for premenopausal patients who require the preservation of ovarian function, the normal appearance of the ovaries can be retained during the operation after screening, and the ovaries can be displaced during the operation (such as intraperitoneally or at the high position of the retroperitoneal paracolic groove) to avoid the need for supplementary pelvic radiotherapy after the operation to damage the ovarian function.

Postoperative supplementary radiotherapy was performed according to the risk factors of recurrence. Tangential border involvement, parastatal infiltration, and positive lymph node metastasis are risk factors for recurrence, and postoperative radiotherapy should be completed for patients with any of these risk factors. Lymphatic vascular space infiltration, tumor diameter > 4cm, and deep cervical interstitial infiltration are all risk factors for recurrence. Patients with any two of these factors should be supplemented with radiotherapy.

2.3 Definition of Chemotherapy Efficacy

According to the results of clinical physical examination combined with pelvic CT/MRI, the therapeutic effects were classified as follows: 1) complete re-mission (CR): complete disappearance of tumor lesion after NACT; 2) partial response (PR): After NACT, the product of maximum and minimum tumor diameter was reduced by more than 50% compared with before chemotherapy, and no new lesions were confirmed. 3) stable disease (SD): After NACT, compared with before chemotherapy, the product of maximum and minimum diameter of the tumor decreased by less than 50% or increased by less than 25%; 4) progressive disease (PD): After NACT, the product of maximum diameter and minimum diameter of the tumor increased by > 25% compared with that before chemotherapy, or new lesions were confirmed.

Patients with complete response and partial response were defined as effective chemotherapy, while patients with stable disease and disease progression were defined as ineffective chemotherapy.

2.4 Statistical Analysis

All statistical analyses in this study were performed using SPSS26.0 statistical software. Measurement data were expressed as mean ± standard deviation; Count data were expressed as frequency (percentage), and chi-square test was used for comparison between groups. Survival curves were plotted using the Kaplan-Meier method, PFS were estimated, and comparison between groups was performed using the log-rank test. Univariate analysis was conducted by COX proportional risk regression model, and variables with $p < 0.05$ in the univariate regression model were included in multivariate analysis to evaluate the risk factors affecting prognosis. $p < 0.05$ was considered to be statistically significant.

3 Results

3.1 Basic Clinical Information

Finally, 263 patients with cervical cancer were included in this study, including 59 patients without supplementary radiotherapy and 204 patients with supplementary radiotherapy. The baseline characteristics of the patients

are shown in Table 1. The median age of patients in the non-radiotherapy group was 51 years (26-74 years), the median course of disease was 4.00 months (0.33 to 60.00 months), and the median SCC level was 2.45 ng/ml (0.50 to 38.70 ng/ml). The median age of patients in the supplemental radiotherapy group was 53 years (24-73 years), the median course of disease was 4.00 months (0.07-96.00 months), and the median SCC water was 5.35 ng/ml (0.50-118.10 ng/ml). The stage of patients in the supplementary radiotherapy group was late, and imaging suggested that there were more patients with positive lymph nodes, and there was no significant difference in HPV infection between the two groups.

Table 1 Baseline characteristics of the group without and with supplementary radiotherapy

characteristics	**no radiotherapy (n=59)**	**radiotherapy (n=204)**
median age (years)	51 (26-74)	53 (24-73)
median course of disease (months)	4.00 (0.33-60.00)	4.00 (0.07-96.00)
median SCC (ng/ml)	2.45 (0.50-38.70)	5.35 (0.50-118.10)
neoplasm staging		
IB3	10 (16.9%)	7 (3.4%)
IIA2	13 (22.0%)	49 (24.0%)
IIB	30 (50.8%)	91 (44.6%)
IIIC1r	6 (10.2%)	57 (27.9%)
ECOG score		
0	38 (64.4%)	124 (60.8%)
1	21 (35.6%)	80 (39.2%)
tumor diameter (cm)		
≤4	21 (35.6%)	63 (30.9%)
＞4	38 (64.4%)	141 (69.1%)
HPV infection status		
negative	3 (5.6%)	12 (6.7%)
non-16/18 type positive	9 (16.7%)	40 (22.3%)
16/18 type positive	42 (77.8%)	127 (70.9%)
radiographic lymph node status		
negative	53 (89.7%)	147 (72.1%)
positive	6 (10.2%)	57 (27.9%)

3.2 Pathological Characteristics

The surgical and pathological data of all patients were shown in Table 2. Tumor diameter was larger in both groups ($p > 0.05$). In the supplemental radiotherapy group, only 2 patients (1.0%) had positive parastatal infiltration, 2 patients (1.0%) had positive incisal margin, and 51 patients (25.0%) had positive lymph nodes. Compared with patients who did not receive supplementary radiotherapy after surgery, patients with lymphatic vasculature space infiltration and cervical deep interstitial infiltration accounted for a larger proportion of patients receiving radiotherapy after surgery, and the difference between the two groups was statistically significant ($p < 0.05$).

Table 2 Surgical and pathological data of the group without and with supplementary radiotherapy

characteristic	**no radiotherapy (n=59)**	**radiotherapy (n=204)**	**P value**
Parastatal infiltration			0.312*
negative	59 (100.0%)	202 (99.0%)	
positive	0	2 (1.0%)	
Incisal margin			0.312*
negative	59 (100.0%)	202 (99.0%)	
positive	0	2 (1.0%)	
Lymph node status			0.000
negative	59 (100.0%)	153 (75.0%)	
Positive	0	51 (25.0%)	
Tumor diameter (cm)			0.494
≤4	21 (35.6%)	63 (30.9%)	
>4	38 (64.4%)	141 (69.1%)	
Lymphatic vasculature			0.000

characteristic	no radiotherapy (n=59)	radiotherapy (n=204)	P value
Negative	58 (98.3%)	160 (78.4%)	
Positive	1 (1.7%)	44 (21.6%)	
Deep cervical interstitial			0.000
Negative	55 (93.2%)	67 (32.8%)	
Positive	4 (6.8%)	137 (67.2%)	

* Likelihood ratio

3.3 Survival Outcomes

In this study, a total of 19 patients (7.22%) were lost to follow-up, and the median follow-up time was 25 months (3-59 months) in the group without supplemental radiotherapy and 25.5 months (3-59 months) in the group with supplemental radiotherapy. In the group without supplemental radiotherapy, 1 patient (1.70%) had relapse within 2 years, and no patient died within 2 years. In the supplemental radiotherapy group, 5 patients (2.45%) developed relapse within 2 years, of which 1 patient (0.49%) had distant metastasis (lung), and 4 patients (1.96%) died within 2 years. As shown in Table 3.

Table 3 Recurrence and death in the group without and with supplementary radiotherapy.

	no radiotherapy	radiotherapy
recurrence	1 (1.70%)	5 (2.45%)
Death	0	4 (1.96%)

The survival curve of patients is shown in Figure 2. The 2-year PFS rate was close (98.10% VS 98.90%) between the supplemental radiotherapy group and the non-supplemental radiotherapy group, and the difference was not significant (p=0.606).

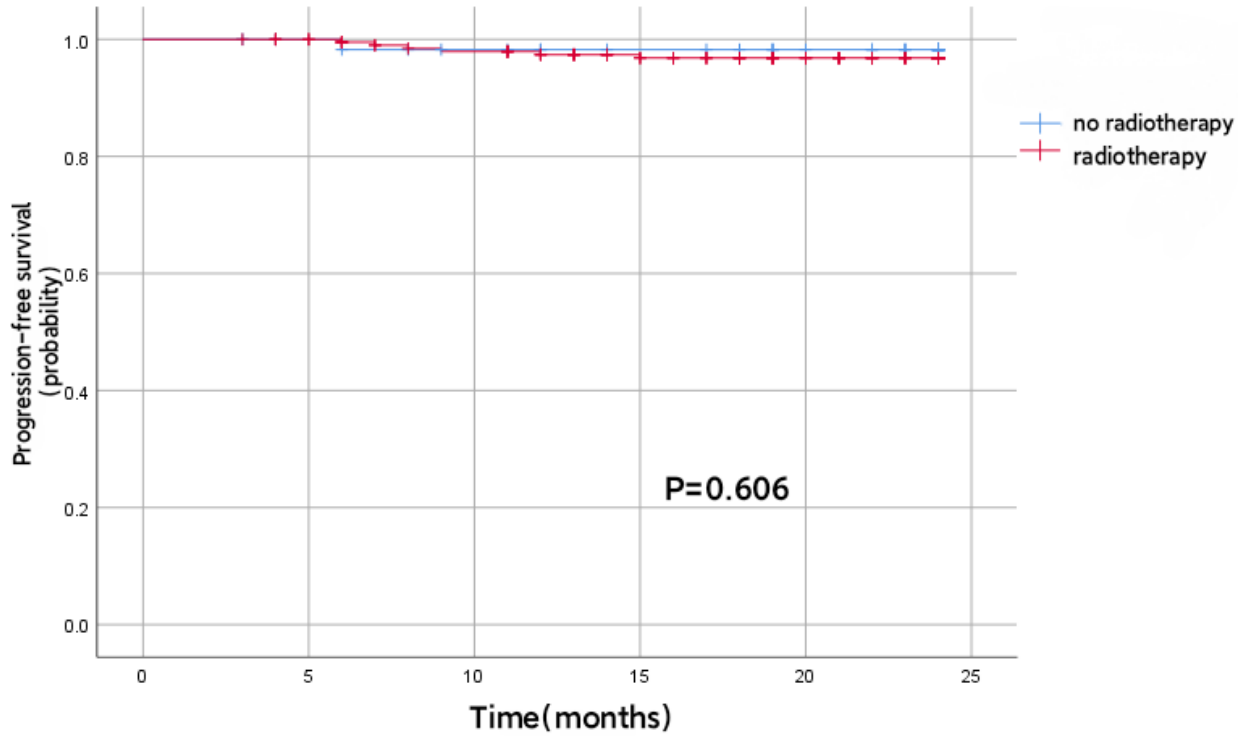

Figure 2 Comparison of 2-year PFS between the group with and without supplementary radiotherapy

The patient's tumor stage, tumor diameter, SCC level, imaging status of lymph node metastasis, pathological status of lymph node metastasis, parastatal involvement, lymph vascular space infiltration, and deep cervical interstitial infiltration were included in univariate Cox regression analysis, and the results were shown in Table 4. All variables with P values < 0.05 in the univariate analysis were included in the multivariate analysis, and the results were shown in Table 5. Cox risk regression showed that parastatal infiltration and lympho-vascular space infiltration were risk factors for 2-year PFS, but only lympho-vascular space infiltration was an

independent risk factor for PFS.

Table 4 Univariate analysis of the influencing factors of 2-year PFS

characteristic	**HR (95% CI)**	**P value**
Tumor staging	3.427 (0.412-28.466)	0.254
Tumor diameter	0.611 (0.137-2.731)	0.519
SCC level	0.382 (0.074-1.970)	0.250
Lymph node status (imaging)	1.269 (0.243-6.543)	0.776
Lymph node status (pathology)	3.125 (0.699-13.967)	0.136
Parastatal infiltration	19.914 (2.397-165.478)	0.006
Lymphatic vascular	6.344 (1.420-28.349)	0.016
Deep interstitial infiltration	5.443 (0.655-45.217)	0.117

Table 5 Multivariate analysis of the influencing factors of 2-year PFS

characteristic	**HR (95% CI)**	**P value**
Parastatal infiltration	6.640 (0.690-63.878)	0.101
Lymphatic vascular	4.996 (1.008-24.756)	0.049

4 Discussion

Cervical cancer is one of the common malignant tumors in women. The cause of most cervical cancer is continuous infection of high-risk human papillomavirus [4]. In the early stage of the disease, patients with cervical cancer generally have no obvious clinical symptoms. As the disease worsens, patients may develop post-coitus hemorrhage, abnormal leucorrhea (such as hemorrhagic leucorrhea), or corresponding symptoms caused by tumor invasion of other organs, such as nonspecific symptoms such as bloody stool, hematuria, hemoptysis, etc. In developing countries such as China, many patients are initially seen in LACC, because cervical cancer screening and vaccination are not yet in place. LACC is often considered to have high risk pathological risk factors such as pelvic lymph node metastasis, parastatal invasion and large tumor diameter.

CCRT is still recommended for patients with LACC. However, many developing countries and regions are not equipped with sufficient radiotherapy equipment and complete radiotherapy procedures. In addition, radiotherapy often leads to pelvic tissue damage. For patients with poor response to radiotherapy, it is difficult to resect the tumor again and guarantee the prognosis. Therefore, NACT-RS therapy is often used in place of CCRT. At present, the efficacy of NACT has been widely recognized in clinical practice, and its advantages are reflected in that NACT can reduce tumor volume, reduce tumor load, obtain surgery opportunities for patients, and reduce the difficulty of surgery to a certain extent. In addition, NACT can also benefit patients in improving peripheral uterine and vaginal invasion and improving subclinical metastatic lesions. However, there are also some opinions that NACT will prolong the treatment time of patients, and for patients who are not sensitive to NACT, treatment may be delayed and the disease may progress, so as to miss the appropriate treatment opportunity. Moreover, NACT will cover up the original pathological risk factors and affect the evaluation of subsequent complementary therapy.

Many studies have concluded whether NACT improves the prognosis of patients. Zeng [5] evaluated the efficacy of NACT on patients with stage IB3 and stage IIA2 cervical cancer by comparing the two treatment methods of CCRT and Next-RS, and observed the 5-year survival rate and complication rate of patients in the two groups. The results showed that the survival period of patients treated with Next-RS was similar to that of patients receiving CCRT. And the side effects do not increase. The study of Gadducci [6] showed that in terms of PFS in patients with stage IB-II cervical cancer, CCRT was superior to post-NACT radical surgery. There are also research results showing that NACT can significantly improve the curative effect of patients and prolong the survival cycle of patients [7, 8].

By grouping all patients with or without postoperative supplementary therapy, this study concluded that surgical treatment after NACT in patients with LACC can reduce the rate of postoperative supplementary radiotherapy while maintaining the same PFS. Mousavi [9] demonstrated that NACT-RS could reduce the need for postoperative radiotherapy in LACC patients. Huang [10] compared the clinical data and survival prognosis of the two groups of patients with NACT-RS and direct surgery,

indicating that NACT reduced the pathological risk factors and the use of radiotherapy in LACC patients without affecting survival, which may protect young patients from radiation-related side effects and thus improve the quality of life. This is consistent with our findings.

Studies have shown that tumor diameter is associated with prognosis. For locally advanced cervical cancer with CCRT, large tumor diameter and non-HPV16/18 genotypes are independently associated with poor PFS [5, 11, 12], also there is a study suggest that HR-HPV infection was not a prognosticator of 5-year OS [13]. In this study, large tumor diameter and HPV infection were not found to be independent risk factors affecting PFS, which may be because the included patients in this study were cervical cancer patients receiving NACT, and tumor diameter was large, so the difference of tumor diameter and HPV infection had no significant effect on prognosis.

It has been reported that the recurrence rate of cervical cancer can reach 60% [14] after initial treatment. The low recurrence rate in this study may be related to the short follow-up time, but the possibility that NACT can improve the prognosis of patients cannot be excluded.

Many studies analyzed prognostic factors, suggesting that for patients receiving NACT-RS, age, the number of lymph node metastases, focal diameter, LVSI, and disease stage are all prognostic factors [15-18]. In this study, the patients' tumor stage, tumor diameter, SCC level, imaging lymph node status, parastatal involvement, pathological lymph node metastasis status, LVSI and deep cervical interstitial infiltration were included in Cox risk regression, and the results showed that parastatal infiltration and LVSI were risk factors affecting 2-year PFS. But only LVSI was an independent risk factor for PFS.

Nowadays, in clinical practice, in addition to surgery, radiotherapy and chemotherapy can be used in the treatment of cervical cancer, new therapeutic methods such as targeted therapy and immunotherapy are also gradually promoted, especially in the treatment of advanced and recurrent cervical cancer. Ota [19] showed that tumor mutation load was a potential prognostic factor for poor prognosis in patients with radical radiotherapy for cervical cancer, which provided a theoretical basis for the treatment of cervical cancer with high tumor mutation load by immune checkpoint inhibitor combined with radiotherapy. Yun [20] showed that cisplatin based chemotherapy could increase the expression of PD-L1 in cervical cancer, providing a basis for immunotherapy combined with NACT. A study from Japan suggests that pembrolizumab plus chemotherapy with or without bevacizumab may prolong survival versus placebo plus chemotherapy with or without bevacizumab and had a manageable safety profile in Japanese patients with persistent, recurrent, or metastatic cervical cancer [21].

There are some limitations in our study. First of all, this study is a retrospective, single-center study with limited sample size, and the selection of samples may lead to bias, so the evidence level value is not as good as multi-center, prospective randomized controlled studies. Secondly, the follow-up time of this study was only 2 years, so the overall survival could not be assessed. Follow-up should be continued in the future to improve the 5-year analysis of PFS and OS. Finally, as the common pathological type of cervical cancer is squamous cell carcinoma, and squamous cell carcinoma is sensitive to radiotherapy and chemotherapy, only cervical squamous cell carcinoma patients are included in this study. Further analysis of adenocarcinoma and other types will be carried out in the future, so as to achieve a more comprehensive and accurate study.

5 Conclusion

NACT can also reduce the occurrence of radiotherapy in addition to obtaining the opportunity of surgery, so as to improve the quality of life of patients without affecting survival. Meanwhile, LVSI is an independent risk factor for progression-free survival in patients with locally advanced cervical cancer who receive NACT. For such patients, complementary treatment after surgery is more helpful to ensure prognosis.

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