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ORIGINAL ARTICLE

Effect of postoperative sequential chemoradiotherapy and concurrent chemoradiotherapy in treating advanced endometrial cancer

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Summary

Purpose: *To evaluate the efficacy and safety of the sequential chemoradiotherapy mode of chemotherapy-radiotherapy-consolidation chemotherapy and the concurrent chemoradiotherapy after operation for advanced (stage III-IV) endometrial cancer.*

Methods: *A total of 116 patients with stage III-IV endometrial cancer were divided into the Sequential group (n=58) and the Concurrent group (n=58) according to the different modes of postoperative adjunctive therapy. The levels of tumor markers in the serum and the occurrence of adverse reactions were compared between the two groups, and the survival and progression of the patients were followed up and recorded. Moreover, the factors influencing the tumor progression in patients were analyzed.*

Results: *The levels of serum carcino-embryonic antigen (CEA), cancer antigen (CA) 125, CA19-9 and adiponectin (APN) declined markedly after treatment with chemoradiotherapy in both groups compared with those before treatment (p<0.05). The median survival was 49.4±4.5 months and 47.9±4.0 months, and the median progression-free survival (PFS) was 47.1±4.6 months and 45.8±4.3 months, respectively, in the Sequential group and the Concurrent group. Besides, the 3-year overall survival (OS) rate in the Sequential group and the Concurrent group was 82.8% and 70.7%, respectively, and the 3-year PFS rate in the two groups was 79.3% and 58.6%, respectively. The 5-year OS rate was 60.3% and 48.3%, and the 5-year PFS rate was 51.7% and 32.8% in the two groups, respectively. Log-rank test indicated that the PFS in the Sequential group was evidently superior to that in the Concurrent group (p=0.017). The results of univariate and multivariate analyses manifested that surgical-pathological stage and postoperative Sequential chemoradiotherapy were independent risk factors for tumor progression in patients with advanced endometrial cancer.*

Conclusions: *Compared with the concurrent chemoradiotherapy, the sequential chemoradiotherapy can prominently delay the progression of advanced endometrial cancer, induce no apparent adverse reactions and has good tolerance. Low surgical-pathological stage and postoperative sequential chemoradiotherapy are independent protective factors against tumor progression.*

Key words: *sequential chemoradiotherapy, concurrent chemoradiotherapy, advanced endometrial cancer*

Introduction

Endometrial cancer, a common gynecological malignancy, accounts for 25-33% of all the malignant tumors of female genital tract [1,2]. About 15% of endometrial cancer patients have had pelvic metastasis or retroperitoneal lymph node metastasis (stage III) when definitely diagnosed, with a 5-year survival rate of 62-73%. In addition, approximately 5% of the patients have bladder involvement, rec-

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tal metastasis or distant metastasis (stage IV), and their median survival is 10-25 months. However, the median survival of the patients with relapsed disease is merely 10 months [3,4].

Currently, the modes of adjuvant chemoradiotherapy after operation for endometrial cancer mainly include concurrent chemoradiotherapy and sequential chemoradiotherapy [5,6]. Secord et al [7] searched and discovered that the postoperative sequential chemoradiotherapy for patients with advanced endometrial cancer can improve their 3-year overall survival (OS) rate (88%) and 3-year progression-free survival (PFS) rate (69%), and possesses similar side effects to other modes of adjuvant chemoradiotherapy after operation. Another study [8] demonstrated that the sequential chemoradiotherapy for patients with high-risk (stage II, III and IV) endometrial cancer have favorable PFS and OS rates as well as tolerable side effects. Therein, the 1-, 3- and 5-year PFS rates were 100%, 80% and 74%, respectively, and the 1-, 3- and 5-year OS rates were 100%, 88% and 79%, respectively [8]. In our study, the clinical data of 116 patients with advanced endometrial cancer were retrospectively analyzed in this research, so as to investigate the efficacy and safety of the sequential chemoradiotherapy and the concurrent chemoradiotherapy after operation for advanced endometrial cancer, thereby providing basis for the formulation of clinical treatment strategies for such patients.

Methods

General data

The clinical data of 116 patients with advanced endometrial cancer admitted to and treated in our hospital from September 2017 to March 2019 were collected. The inclusion criteria were as follows: 1) The patients had surgical-pathological stage III and IV endometrial cancer based on the staging criteria of the International Federation of Gynecology and Obstetrics (FIGO) in 2009 [9]. 2) The patients underwent comprehensive operation with a scope of total hysterectomy+bilateral adnexectomy+pelvic and para-

Table 1. Baseline characteristics of the studied patients

Characteristics	*Sequential group (n=58) n (%)*	*Concurrent group (n=58) n (%)*	*p value*
Age (years)	56.6±9.6	57.9±9.7	0.470
Pathological type			0.507
Endometrioid adenocarcinoma	47 (81.0)	43 (74.1)	
Papillary serous cystadenocarcinomas	10 (17.2)	12 (20.7)	
Clear cell carcinoma	1 (1.7)	3 (5.2)	
FIGO stage			0.889
IIIa	13 (22.4)	10 (17.2)	
IIIb	17 (29.3)	15 (25.9)	
IIIc	22 (37.9)	25 (43.1)	
IVa	5 (8.6)	6 (10.3)	
IVb	1 (1.7)	2 (3.4)	
Differentiation grade			0.812
Low	18 (31.0)	21 (36.2)	
Moderate	27 (46.6)	26 (44.8)	
High	13 (22.4)	11 (19.0)	
Chemotherapy regimens			0.531
AP	28 (48.3)	23 (39.7)	
TC	15 (25.9)	13 (22.4)	
TP	12 (20.7)	16 (27.6)	
CAP	3 (5.2)	6 (10.3)	
Chemotherapy cycles			0.337
<6	34 (58.6)	39 (67.2)	
≥6	24 (41.4)	19 (32.8)	

FIGO: International Federation of Gynecology and Obstetrics; AP: Doxorubicin+ Cisplatin; TC: Taxol+Carboplatin; TP: Taxol+Cisplatin; CAP: Cyclophosphamide+ Doxorubicin+ Cisplatin

aortic lymphadenectomy+pelvic and abdominal lesion resection. 3) The pelvic and para-aortic lymphadenectomy must be performed simultaneously for the patients with stage III endometrial cancer who received initial operation, while the patients having distant metastasis were not required to receive retroperitoneal lymphadenectomy. 4) The patients had a life expectancy longer than 3 months. The exclusion criteria included the patients with stage I and II endometrial cancer, those not treated with comprehensive operation, those with severe cardiac, hepatic or renal dysfunction, or those complicated with coagulation disorders, immune system disorders, other tumors or neurological dysfunction. According to the treatment protocols, all the patients were assigned into the Sequential group (sequential chemoradiotherapy, n=58) and the Concurrent group (concurrent chemoradiotherapy, n=58). The patients were aged 26-74 years, with an average age of 57.2±9.7 years. There were no statistically significant differences in the clinical baseline data such as age, pathological type, FIGO stage, grade of tumor differentiation, chemotherapy regimen and chemotherapy cycle between the two groups (p>0.05), which were comparable (Table 1). The *Declaration of Helsinki* was followed, the duty of disclosure was performed, and all the patients enrolled signed the informed consent form. This study was approved by the Ethics Committee of Hubei Provincial Hospital of Traditional Chinese Medicine.

Therapeutic methods

The chemotherapy regimens adopted after operation primarily included doxorubicin+cisplatin (AP) regimen (40-60 mg/m^2 doxorubicin and 70-75 mg/m^2 cisplatin), paclitaxel+carboplatin (TC) regimen (135-175 mg/m^2 paclitaxel and area under receiver operating characteristic curve of carboplatin=5), doxorubicin+cisplatin+cyclophosphamide (CAP) regimen (40-60 mg/m^2 doxorubicin, 70-75 mg/m^2 cisplatin and 500-600 mg/m^2 cyclophosphamide) and paclitaxel+cisplatin (TP) regimen (135-175 mg/m^2 paclitaxel and 70-75 mg/m^2 cisplatin).

The radiotherapy could be classified as external beam radiotherapy and brachytherapy for vaginal stump. The marker positions at the abdomen, pelvic cavity and upper femur were fixed using vacuum bags, the central scanning spot of computed tomography (CT) was labeled, and pessaries were placed into the marker positions for scanning. Next, large aperture spiral CT (Philips) was used for simulation positioning, in which the slice thickness was 3 mm, the superior margin of the first lumbar vertebra was set as the upper border, and the site at 3-5 cm below the inferior margin of ischial tuberosity was taken as the lower border. As for the definition of target regions, gross tumor volume (GTVtb) referred to the regions of primary tumors, including the vagina, cervix and uterus, and clinical target volume (CTVtb) included the GTVtb and the whole pelvic lymphatic drainage region. The organs at risk (OAR) involved the urinary bladder, femoral head, spinal cord, small intestine, rectum and hip bone. A linear accelerator (Siemens) with 6 MV X-ray was utilized for 3-dimensional conformal radiotherapy (3-D CRT) *via* four-field box irradiation (prescribed dose: 50.4-56.0 Gy) or intensity modulated radiation therapy (IMRT) *via* five-field irradiation (prescribed dose: 1.8-2.0 Gy) for 5 times a week. The planned irradiation region was covered by 95% isodose curves, on which the irradiation dose was less than 10% lower or higher than the prescribed dose. Besides, over 98% of the irradiation region was covered by the prescribed dose.

The patients in the Sequential group were treated with 1-4 cycles of chemotherapy. After that, external beam radiotherapy and brachytherapy for vaginal stump were performed, and 1-4 cycles of the same consolidation chemotherapy regimen were implemented subsequently. In the Concurrent group, 3-6 cycles of chemotherapy were administered after operation, followed by external beam radiotherapy and brachytherapy for vaginal stump.

Observation indexes

The chemotherapy side effects were evaluated according to the WHO grading standards for side effects of anti-cancer drugs. The radiotherapy side effects included radiation enteritis and urological side effects. The changes in serum levels of carcino-embryonic antigen (CEA), cancer antigen (CA) 125, CA19-9 and adiponectin (APN) before and after treatment in the two groups were compared. Specifically, 4 mL of fasting venous blood was drawn before and after treatment and centrifuged to separate the serum. Later, the serum was stored in a refrigerator at -45°C for detection of the expression levels of CEA, CA125, CA19-9 and APN *via* enzyme-linked immunosorbent assay (ELISA).

The follow-up time was set as follows: the patients were reexamined by CT scan of the pelvic cavity or magnetic resonance imaging (MRI) every 3 months in the 1-2 years after treatment, and they were reexamined by B-mode ultrasound every 6 months. Two years later, cytological examination of vaginal smears was reexamined every 6-12 months, and the CT scan of the pelvic cavity or MRI reexamination was performed once a year. The patients were followed up till December 2019, and their survival and disease progression were recorded. The PFS was defined as the time interval from the start of treatment to the first occurrence of PD or death due to any reason, and the OS referred to the time interval from the start of chemotherapy to the death or last follow-up.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was used for statistical analyses. The measurement data were expressed by mean ± standard deviation, and two-sample t-test was performed for comparison between groups. The enumeration data were presented as ratio (%), and x^2 test was performed for comparison between groups. Kaplan-Meier method was applied to plot the survival curves, log-rank test was utilized to assess survival differences between two groups, while the factors influencing patient survival were evaluated with univariate and multivariate Cox analysis proportional hazards regression model. P<0.05 suggested that the difference was statistically significant.

Results

Comparison of incidence of adverse reactions between the two groups of patients

The common adverse reactions related to chemoradiotherapy mainly included vaginal bleeding, bone marrow suppression, hepatic function damage, renal function damage, gastrointestinal reactions, peripheral neuritis and radiotherapy side effects. Among them, the bone marrow suppression was primarily manifested as decrease in hemoglobin, white blood cells and platelets (grade I-II), which were improved after symptomatic treatment. The difference in the incidence rate of adverse reactions was not statistically significant between the two groups of patients (p>0.05) (Table 2).

Changes in expressions of CEA, CA125, CA19-9 and APN in the two groups of patients

No statistically significant differences in the levels of CEA, CA125, CA19-9 and APN were observed between the two groups before treatment (p>0.05), and all those indexes were decreased remarkably after treatment in both groups compared with those before treatment (p<0.05). After treatment, there was no statistically significant difference in the CEA level between the two groups (p=0.252), while the Sequential group had notably lower levels of CA125, CA19-9 and APN than the Concurrent group (p=0.044, p=0.011, p=0.009) (Table 3).

Follow-up results of patient survival

As of December 2019, the mean follow-up was 46.1±7.7 months and 45.3±7.1 months in the two groups. The mean survival was 49.4±4.5 months and 47.9±4.0 months in the Sequential group and the Concurrent group, respectively, and the mean PFS was 47.1±4.6 months (Sequential group) and 45.8±4.3s months (Concurrent group), respectively. Moreover, in the Sequential group and the Concurrent group, the 3-year OS rate was 82.8% (48/58) and 70.7% (41/58), respectively, and the 3-year

Table 2. Comparison of adverse reactions of patients in the two studied groups

Adverse reactions	*Sequential group (n=58) n (%)*	*Concurrent group (n=58) n (%)*	*p value*
Vaginal bleeding	4 (6.9)	5 (8.6)	0.729
Bone marrow suppression	19 (32.8)	14 (24.1)	0.304
Nausea, vomiting	6 (10.3)	5 (8.6)	0.751
Diarrhea	4 (6.9)	6 (10.3)	0.508
Hepatic function damage	8 (13.8)	5 (8.6)	0.377
Renal function damage	7 (12.1)	4 (6.9)	0.342
Peripheral neuritis	1 (17.2)	0 (0)	0.315
Radiotherapy side effect	5 (8.6)	3 (5.2)	0.464

Table 3. Comparison of tumor markers of patients in the two studied groups

Tumor markers	*Sequential group (n=58)*	*Concurrent group (n=58)*	*p value*
CEA (μg/L)			
Pretreatment	26.77±5.54	27.81±5.90	0.330
Posttreatment	13.68±3.69	14.43±3.31	0.252
CA125 (U/ml)			
Pretreatment	64.74±12.26	63.55±11.73	0.594
Posttreatment	31.29±6.82	33.62±6.05	0.044
CA19-9 (U/ml)			
Pretreatment	77.18±15.22	78.08±16.24	0.758
Posttreatment	35.95±6.88	38.79±7.46	0.011
APN (μg/ml)			
Pretreatment	5.65±1.03	5.37±0.99	0.138
Posttreatment	8.21±0.87	7.76±0.94	0.009

CEA: Carcinoembryonic antigen; CA125: ovarian cancer antigen 125; APN: Adiponectin

PFS rate was 79.3% (46/58) and 58.6% (34/58), respectively. The 5-year OS rate was 60.3% (35/58) (Sequential group) and 48.3% (28/58) (Concurrent group), and the 5-year PFS rate was 51.7% (30/58) (Sequential group) and 32.8% (19/58) (Concurrent group), respectively. The survival curves in the two groups were plotted using Kaplan-Meier method, and log-rank test showed that the OS exhibited no statistically significant difference between the two groups of patients (p=0.112), while the PFS in the Sequential group was evidently superior to that in the Concurrent group (p=0.017) (Figure 1).

Univariate analysis results of tumor progression in patients with advanced endometrial cancer

The possible influencing factors for the tumor progression in patients with advanced endometrial cancer, such as age, pathological type, surgical-pathological stage, postoperative therapeutic mode, chemotherapy cycles and chemotherapy regimens, were included into the univariate analysis. The results manifested that the surgical-pathological stage and postoperative adjunctive therapy mode were risk factors for tumor progression in pa-

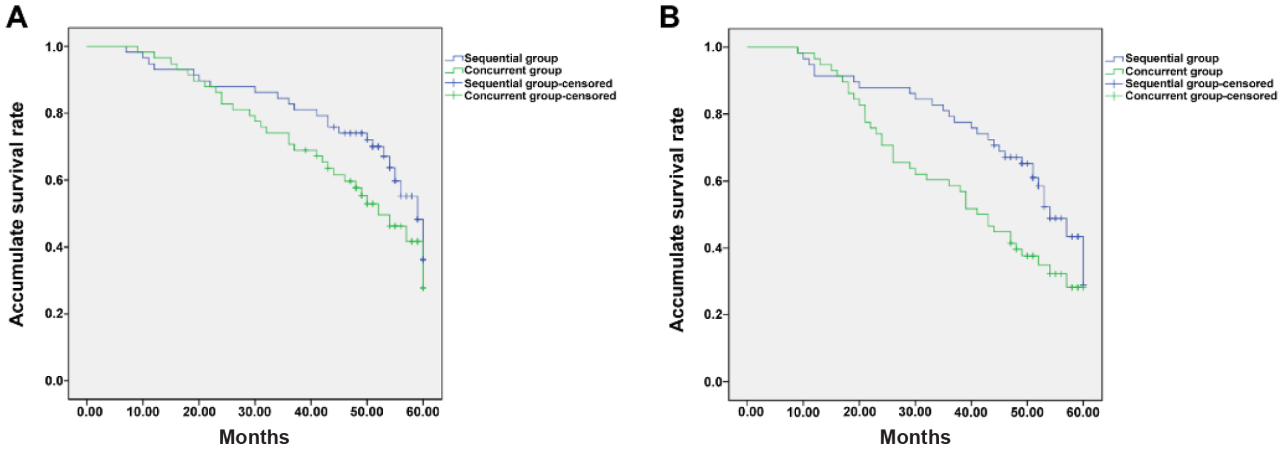

Figure 1. Kaplan-Meier survival curves of advanced endometrial carcinoma patients. The difference between overall survival rate **(A)** of patients in the Sequential group and the Concurrent group had no statistical significance (p=0.112). The progression-free survival rate **(B)** of patients in the Sequential group was significantly higher than that of the Concurrent group (p=0.017).

Table 4. Univariate analysis of predictors for prognosis of patients with advanced endometrial cancer

Predictors	*Cases*	*5-year PFS %*	*p value*
Age, years			0.053
≤ 60	76 (65.5)	48.7	
> 60	40 (34.5)	30.0	
Pathological type			0.392
Endometrioid adenocarcinoma	90 (77.6)	45.6	
Papillary serous cystadenocarcinomas	22 (19.0)	31.8	
Clear cell carcinoma	4 (3.4)	25.0	
Surgical-pathological stage			0.015
III	105 (90.5)	44.8	
IV	11 (9.5)	18.2	
Postoperative therapeutic mode			0.039
Sequential chemoradiotherapy	58 (50.0)	51.7	
Concurrent chemoradiotherapy	58 (50.0)	32.8	
Chemotherapy regimens			0.351
AP	51 (44.0)	51.0	
TC	28 (24.1)	32.1	
TP	28 (24.1)	35.7	
CAP	9 (7.8)	44.4	

Table 5. Multivariate logistic regression analysis of predictors for prognosis of patients with advanced endometrial cancer

Parameters	*OR value*	*95% CI*	*p value*
Surgical-pathologic stage IV	2.027	1.313-8.890	0.028
Postoperative Sequential chemoradiotherapy	0.897	0.525-0.959	0.011

OR: Odds Ratio; CI: Confidence interval

tients with advanced endometrial cancer (p=0.015, p=0.039) (Table 4).

Furthermore, the factors with statistical significance in the univariate analysis, including the surgical-pathological stage and postoperative sequential chemoradiotherapy, were subjected to multivariate analysis which revealed that both indexes were the independent risk factors for the tumor progression in patients with advanced endometrial cancer [odds ratio (OR) =2.027, 95% confidence interval (95% CI) =1.313-8.890, p=0.028, and OR=0.897, 95% CI =0.525-0.959, p=0.011] (Table 5).

Discussion

Endometrial cancer is a very common malignancy of the female reproductive system, whose morbidity rate is second only to that of cervical cancer in China. Most patients are diagnosed early due to symptoms such as irregular vaginal bleeding, but 25-35% of them are in advanced stage when diagnosed, making it very difficult to be treated [10].

The operation combined with radiotherapy and/or chemotherapy is the major therapeutic method for endometrial cancer, resulting in a 5-year OS of 67%. The operation can be divided into stage I (complicated with poor differentiation and deep myometrial invasion), II and III (high-risk endometrial cancer), and the patients in stage II-III cannot be cured by operation alone [11]. Studies have elucidated that, in contrast to whole-pelvic irradiation, the postoperative adjuvant chemotherapy can improve the survival rate of patients with advanced endometrial cancer more preferably, but pelvic recurrence occurs in 18-47% of the endometrial cancer patients undergoing chemotherapy alone after operation [12,13]. In the GOG 122 study, a randomized phase III clinical study, the therapeutic effects of the AP chemotherapy regimen and whole-pelvic irradiation in advanced endometrial cancer were compared, and the results indicated that the survival rate of patients receiving the AP chemotherapy regimen was 51%, while that of patients treated with whole-pelvic irradiation was 38% [14]. The research conducted by Secord et al demonstrated that the 3-year OS and PFS rates of patients undergoing postoperative adjuvant chemoradiotherapy (79% and 62%, respectively) were higher than those of patients receiving simple postoperative radiotherapy (70% and 59%, respectively) or chemotherapy (33% and 19%, respectively) [15]. According to a study on alternating chemoradiotherapy in 32 cases of high-risk endometrial cancer after operation, 3 cycles of TC chemotherapy regimen, radiotherapy and 3 cycles of the same chemotherapy regimen were administered, and the patients were followed up shorter than 2 years on average. After that, 3 cases of death and 5 cases of recurrence were observed [5]. It can be seen that the radiotherapy is able to control the local tumor recurrence, and the chemotherapy mainly controls the distant tumor metastasis. Therefore, in the case of advanced endometrial cancer with high recurrence and mortality rates as well as tolerable side effects, the postoperative adjunctive therapy mode combined with chemoradiotherapy has irreplaceable advantages [16].

Currently, consensus has been reached on the adjunctive therapy mode combined with chemoradiotherapy after operation for advanced endometrial cancer. It is recommended in the NCCN guideline (Version 2019) that the postoperative care for stage III and IV patients be formulated only based on the stage, without the consideration of pathological differentiation. In other words, the patients in stage IIIa-IVa are treated with external beam radiotherapy±vaginal brachytherapy±chemotherapy, or chemotherapy±vaginal brachytherapy, after operation, and the patients in stage IVb are subjected to postoperative chemotherapy±external beam radiotherapy±vaginal brachytherapy [17]. Nevertheless, the best mode of postoperative adjuvant chemoradiotherapy for the patients with advanced endometrial cancer remains controversial.

Theoretically, the sequential chemoradiotherapy possesses unique advantages, which not only give full play to its efficacy superiority of chemoradiotherapy but also controls relevant side effects of chemoradiotherapy [18]. In a prospective study of Lupe et al, 4 cycles of TC chemotherapy were administered to 33 patients with advanced endometrial cancer, including 7 cases of stage IIIa, 23 cases of stage IIIc and 3 cases of stage IVb, after op-

eration. Subsequently, external pelvic radiotherapy and 2 cycles of chemotherapy were performed. The results manifested that 30 (91%) patients received the scheduled chemotherapy before radiotherapy, only 25 (76%) patients completed the scheduled chemotherapy after radiotherapy, and 9 (27%) patients had grade III-IV side effects due to chemotherapy. All the patients accomplished the pelvic radiotherapy. Among them, 19 (58%) patients were treated with standard four-field radiotherapy, 14 (42%) received intensity-modulated radiotherapy, and 10 (30%) underwent extended field radiotherapy. In addition, there were 4 (12%) cases of grade III-IV radiotherapy side effects, 6 (18%) cases of chronic radiotherapy side effects and no death after treatment. The 2-year PFS and OS rates were both 55%, and merely 1 (3%) case of pelvic recurrence was detected [19].

In this research, the Sequential group had a 3-year OS rate of 82.8% (48/58) and a 3-year PFS rate of 79.3% (46/58), while the Concurrent group exhibited a 3-year OS rate of 70.7% (41/58) and a 3-year PFS rate of 58.6% (34/58). The 5-year OS rate was 60.3% (35/58) and 48.3% (28/58), and the 5-year PFS rate was 51.7% (30/58) and 32.8% (19/58) in the two groups, respectively. No statistically significant difference in the OS was detected between the two groups of patients (p=0.112), while the Sequential group displayed a distinctly longer PFS than the Concurrent group (p=0.017). Besides, the OS rate in this research was higher than the 2-year OS rate (55%) reported by Lupe et al, but basically consistent with the 3-year OS rate (88%) reported by Aoki et al [13, 17]. The incidence rate of adverse reactions showed no statistically significant difference between the two groups of patients (p>0.05), which is identical to the results reported in literature [20]. Based on the results of univariate and multivariate analyses, the surgical-pathological stage and postoperative Sequential chemoradiotherapy were confirmed as independent risk factors for the tumor progression in patients with advanced endometrial cancer (OR=2.027, 95% CI =1.313-8.890, p=0.028, and OR=0.897, 95% CI =0.525-0.959, p=0.011).

Some limitations should be acknowledged in this research, such as limited sample size, short follow-up time, incomprehensive follow-up content, great heterogeneity of chemotherapy regimens and cycles and possible bias in the records of related side effects. Therefore, the conclusion obtained in this research needs to be supported by data from more rigorous and reliable large-sample prospective clinical studies in the future.

Conclusions

Compared with the concurrent chemoradiotherapy, the sequential chemoradiotherapy can prominently delay the progression of advanced endometrial cancer, induce no apparent adverse reactions and result in good tolerance of patients. The low surgical-pathological stage and postoperative sequential chemoradiotherapy serve as independent protective factors for the tumor progression in patients.

Conflict of interests

The authors declare no conflict of interests.

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