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ORIGINAL ARTICLE

Efficacy of postoperative radiotherapy combined with taxol+carboplatin chemotherapy regimens in the treatment of high-risk early-stage endometrial cancer

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Summary

Purpose: *To compare the efficacy and safety of postoperative extrapelvic irradiation intensity-modulated radiotherapy (IMRT)+concurrent chemotherapy and vaginal brachytherapy (VBT)+concurrent chemotherapy in the treatment of patients with high-risk early-stage endometrial cancer, and analyze the influencing factors for the prognosis of patients.*

Methods: *A total of 126 patients with high-risk stage Ic-IIa endometrial cancer were divided into extrapelvic irradiation IMRT + concurrent taxol+carboplatin (TC) chemotherapy group (IMRT group, n=63) and VBT + concurrent TC chemotherapy group (VBT group, n=63). Then, the efficacy and the incidence rate of adverse reactions were compared between the two groups of patients. Additionally, the possible influencing factors for the prognosis of patients were analyzed.*

Results: *In the Functional Assessment of Cancer Therapy-General Version 4 (FACT-G-V4) scale for the quality of life of patients, the scores of physiological status, social/family status, emotional status and functional status were dramatically higher in the VBT group than in the IMRT group at 3 months after treatment. The 5-year overall survival (OS) and progression-free survival (PFS) rates were 87.3% and 73.0% in the IMRT group and 82.5% and 66.7% in the VBT group, respectively. Furthermore, advanced age, lower uterine segment involvement and anemia before treatment were independent risk factors for tumor progression in patients with endometrial cancer.*

Conclusions: *For patients with high-risk early-stage endometrial cancer, postoperative VBT + concurrent TC chemotherapy has similar efficacy to postoperative extrapelvic irradiation IMRT + concurrent TC chemotherapy, but patients receiving the former have fewer adverse reactions and high quality of life. Advanced age, lower uterine segment involvement and anemia before treatment are independent risk factors affecting tumor progression in such patients.*

Key words: *chemotherapy, intensity-modulated radiotherapy, vaginal brachytherapy, endometrial cancer, early stage, efficacy*

Introduction

Endometrial cancer, one of the most common malignancies in females, accounting for 20-30% of malignant tumors in the female reproductive system [1]. Its incidence has increased significantly in recent years, and it tends to be more prevalent in young people. Increasingly more patients have high-risk factors that are the main reasons for recurrence and metastasis of endometrial cancer [2]. For patients with stage lc-IIa endometrial cancer, radical surgery or concurrent chemoradiotherapy can achieve better therapeutic effects. For those with high-risk factors in postoperative pathology, adjuvant chemoradiotherapy is needed [3,4]. Currently, the widely used radiotherapy approaches

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in clinical practice are extrapelvic irradiation and vaginal brachytherapy (VBT), but they have a risk of causing acute toxicity and long-term complications [5]. Most of the acute skin reactions and adverse reactions of gastrointestinal and genitourinary tract after pelvic radiotherapy can be relieved after symptomatic treatment, but more than 20% of patients still suffer from persistent mild complications, including abdominal cramps, diarrhea, colpoxerosis and coleostenosis, affecting the quality of life of patients, and about 3% of females will have severe long-term gastrointestinal complications [6,7].

In this study, the efficacy and safety of postoperative extrapelvic irradiation intensity-modulated radiotherapy (IMRT)+concurrent chemotherapy and VBT+concurrent chemotherapy in the treatment of patients with high-risk stage Ic-IIa endometrial cancer were compared and analyzed, and the potential factors affecting the prognosis of patients were analyzed.

Methods

General data

The clinical data of 126 patients with early-stage endometrial cancer were collected. The inclusion criteria were as follows: 1) patients with surgical pathological stage Ic-IIa endometrial cancer according to the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging criteria [8]; 2) those undergoing total hysterosalpingo-oophorectomy + pelvic lymph node dissection or biopsy, or para-abdominal aortic lymphadenectomy or biopsy in some cases; 3) those with the following high-risk factors confirmed through postoperative pathology: advanced age (over 60 years), deep myometrial invasion, high histological grade (G2-G3), lower uterine invasion, lymphovascular space invasion or incomplete pelvic lymph node dissection; and 4) those with a Karnofski performance status (KPS) >70 points. The exclusion criteria involved: 1) patients who had received anti-tumor therapy such as radiotherapy, chemotherapy and endocrine therapy; 2) those with severe cardiac, pulmonary, hepatic or renal dysfunction; 3) those with coagulation disorders; 4) those with immune system disorders; 5) those complicated by other malignancies; or 6) those with mental disorders. All patients were divided into extrapelvic irradiation IMRT+concurrent TC chemotherapy group (IMRT group, n=63) and VBT+concurrent taxol+carboplatin (TC) chemotherapy group (VBT group, n=63) according to the different therapeutic regimens adopted. The patients enrolled were aged 24-71 years old (mean 54.5±9.7). The general clinical baseline data of patients showed no statistically significant differences between the two groups (p>0.05), which were comparable (Table 1). All patients enrolled were informed of this study and signed the informed consent in accordance with *Declaration of Helsinki*. This study was approved by the Ethics Committee of Yanan University Affiliated Hospital.

Table 1. Baseline characteristics of the studied patients

Parameters	*IMRT group (n=63)* *n (%)*	*VBT group (n=63)* *n (%)*	*p value*
Age (years)	55.6±9.5	53.9±9.8	0.325
Pathological type			0.297
Endometrioid adenocarcinoma	57 (90.5)	52 (82.5)	
Others	6 (9.5)	11 (17.5)	
FIGO stage			0.427
Ic	48 (76.2)	43 (68.3)	
IIa	15 (23.8)	20 (31.7)	
Histological grade			0.368
G2	39 (61.9)	33 (52.4)	
G3	24 (38.1)	30 (47.6)	
Vascular invasion	51 (81.0)	46 (73.0)	0.398
Tumor diameter, cm			0.434
<4	21 (33.3)	16 (25.4)	
≥4	42 (66.7)	47 (74.6)	
Surgical margin (+)	3 (4.8)	2 (3.2)	0.721
Deep muscular invasion	55 (87.3)	49 (77.8)	0.240
KPS score			0.373
70-80	34 (54.0)	28 (44.4)	
80-90	29 (46.0)	35 (55.6)	

IMRT: intensity modulated radiation therapy; VBT: vaginal brachytherapy; FIGO: international federation of gynecology and obstetrics; KPS: Karnofsky performance status.

Therapeutic methods

Total hysterosalpingo-oophorectomy + pelvic lymph node dissection or biopsy were employed for all patients, and para-abdominal aortic lymphadenectomy or biopsy was performed in some of them.

The adjuvant radiotherapy was conducted as follows: Before positioning, patients should suppress the urine and empty the intestine. Cleansing enema could be performed one day in advance if necessary. Then, patients lied on a CT simulation machine in supine position, fixed with body membranes and received enhancement scan with iohexol. The images were uploaded at a slice gap of 5 mm. The scanned area included two parts, namely, the lower abdomen and pelvic cavity, from the first and second lumbar vertebrae to 5-10 cm below the symphysis pubis. The target volume and organ at risk (OAR) delineation, plan design, dose calculation and evaluation were carried out. The target volumes for radiotherapy after surgery for endometrial cancer included clinical target volumes (CTVs) and planning target volumes (PTVs). The CTVs included CTV1 vaginal stump, CTV2 paravaginal and parauterine tissues, and CTV3 total, external and internal iliac lymph node drainage regions. The para-abdominal aortic, presacral and inguinal lymph node drainage regions were included if necessary. The drainage regions of the CTVs were generally delineated 7 mm outward with the accompanying blood vessel as the center. The PTVs included PTV1 (CTV1+15 mm outward), PTV2 (CTV2+10 mm outward) and PTV3 (CTV3+7 mm outward). Besides, normal organs such as the bladder, rectum, small intestine, colon, spinal cord and femoral head were also delineated to limit the dose. The dose of external irradiation was 1.8 Gy/fraction once a day for 25 times (5 courses/week), with a total dose of 45 Gy. For extrapelvic irradiation, IMRT was employed using a 6 MeV linear accelerator. A 192Ir afterloading machine was utilized for vaginal irradiation, and the dose reference point was 0.5 cm below the vaginal mucosa. The supplementary irradiation dose was 18 Gy in total (6 Gy/fraction, once a week, 3 times in total). The limits for OAR dose were as follows: rectum <40 Gy, bladder <40 Gy, maximum dose at the spinal cord <45 Gy.

Concurrent chemotherapy was performed every 3 weeks before, during and after radiotherapy, 3-4 times in total, based on the combined TC chemotherapy scheme. The dose was as follows: paclitaxel 135 mg/m^2+carboplatin (CBP) (AUC4-5). The above scheme for concurrent radiochemotherapy was adopted for all patients in the two groups.

During treatment, blood routine tests and hepatic and renal function indicators of patients were closely observed. In the case of white blood cells <3×10^9/L or platelets <70×10^9/L, the treatment was stopped, and recombinant granulocyte stimulating factor or recombinant human interleukin-11 were given to increase leukocytes or platelets.

Observation indexes

The acute and chronic adverse reactions of the intestinal tract and urinary system were assessed according to the response evaluation criteria after radiotherapy (RTOG/EORTC), and WHO chemotherapeutic drug toxicity classification standard was employed to evaluate the severity of bone marrow suppression. The quality of life score scale [Functional Assessment of Cancer Therapy-General Version 4 (FACT-G-V4)] was adopted to evaluate the quality of life of patients at enrollment and 3 months after treatment, and the changes in FACT-G-V4 scores of the two groups were compared before and after treatment. The FACT-G-V4 scale consists of four items (physiological condition, social/family situation, emotional status and functional status). The lower the score, the higher the quality of life.

All patients were followed up every 3 months within 1 year after treatment and every 6 months thereafter. The survival status and tumor recurrence of patients were recorded. The detection time of local recurrence or pelvic lymph node metastasis in the radiation field was defined as the time for local regional recurrence. The detection time of metastasis to other places was defined as the time for distant metastasis. The time from the day of treatment after surgery to death or from the day of admission to the last follow-up was defined as the overall survival (OS).

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was utilized for statistical analyses. Measurement data were expressed as mean ± standard deviation, and t-test was employed for the comparison between two groups. Enumeration data were expressed as ratio (%), and x^2 test was used for comparison among groups. Survival curves were plotted via Kaplan-Meier method and log-rank test was adopted to verify whether the difference in survival was statistically significant between the two groups, and the Cox proportional hazard regression model was utilized for multivariate analysis of the factors affecting the prognosis of patients. P<0.05 suggested that the difference was statistically significant.

Results

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

The common adverse reactions related to chemoradiotherapy mainly included bone marrow suppression, gastrointestinal reactions, peripheral neurotoxicity, radiation cystitis, radiation enterocolitis and radiation colitis. Among acute adverse reactions, bone marrow suppression was mainly manifested as anemia, leukopenia and thrombocytopenia, which was mostly of grade I-II and relieved after symptomatic treatment. The incidence of radiation enterocolitis and radiation colitis was significantly higher in the IMRT group than in the VBT group (p=0.045, p=0.034), whereas other acute adverse reactions exhibited no statistically signifi-

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

Parameters	*IMRT group (n=63)*		*VBT group (n=63)*		*p value*
	Grade I-II n (%)	*Grade III-IV n (%)*	*Grade I-II n (%)*	*Grade III-IV n (%)*	
Acute adverse reaction					
Leukopenia	19 (30.2)	13 (20.6)	15 (23.8)	9 (14.3)	0.209
Anemia	13 (20.6)	8 (12.7)	10 (15.9)	4 (6.3)	0.233
Thrombocytopenia	16 (25.4)	10 (15.9)	12 (19.0)	7 (11.1)	0.265
Acute radiation cystitis	26 (41.3)	4 (6.3)	23 (36.5)	3 (4.8)	0.591
Acute radiation enterocolitis	36 (57.1)	9 (14.3)	27 (42.9)	7 (11.1)	0.045
Acute radiation colitis	31 (49.2)	6 (9.5)	22 (34.9)	5 (7.9)	0.034
Gastrointestinal reaction	29 (46.0)	3 (4.8)	24 (38.1)	1 (1.6)	0.283
Peripheral neurotoxicity	11 (17.5)	1 (1.6)	8 (12.7)	0 (0)	0.465
Long-term adverse reaction					
Late radiation cystitis	28 (44.4)	4 (6.3)	20 (31.7)	2 (3.2)	0.048
Late radiation enterocolitis	35 (55.6)	8 (12.7)	24 (38.1)	4 (6.3)	0.012
Late radiation colitis	31 (49.2)	3 (4.8)	19 (30.2)	2 (3.2)	0.031

IMRT: intensity modulated radiation therapy; VBT: vaginal brachytherapy.

Table 3. Comparison of FACT-G-V4 scores of patients in the two studied groups

Parameters	*IMRT group (n=63)*	*VBT group (n=63)*	*p value*
Pretreatment			
Physiological status	20.57±3.76	20.88±3.72	0.643
Social / family status	21.12±4.46	21.43±4.28	0.592
Emotional status	18.19±3.87	18.53±4.07	0.532
Functional status	18.37±3.85	18.84±4.15	0.511
Posttreatment			
Physiological status	18.21±4.54	16.69±4.36	0.046
Social / family status	16.36±4.74	14.51±4.83	0.032
Emotional status	15.71±4.49	13.68±3.89	0.008
Functional status	14.34±4.53	12.79±4.81	0.045

IMRT: intensity modulated radiation therapy; VBT: vaginal brachytherapy.

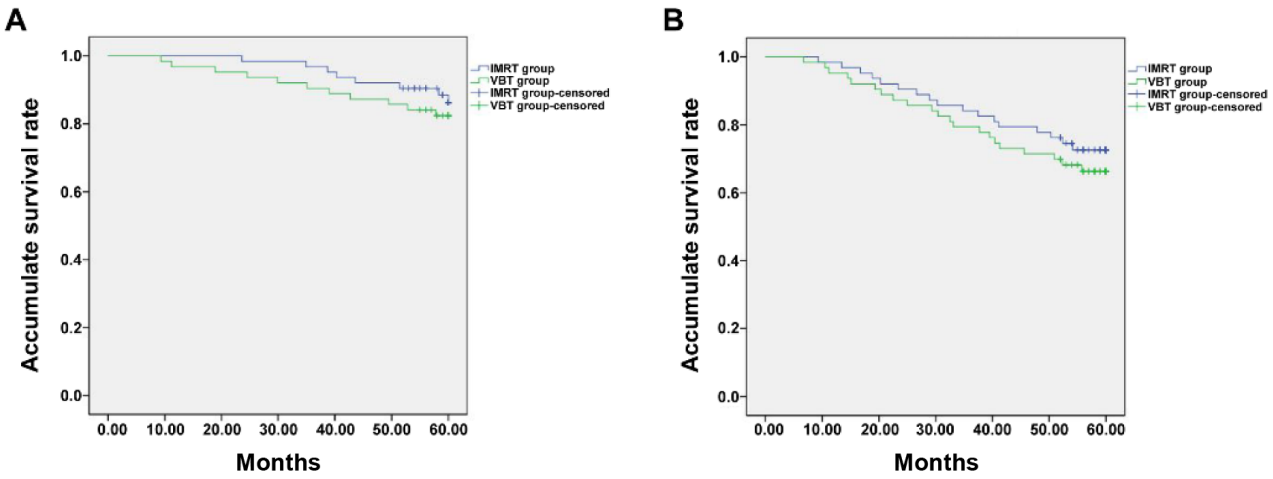

Figure 1. Kaplan-Meier survival curves of endometrial carcinoma patients. **A:** The difference between overall survival rate of patients in IMRT group and VBT group had no statistical significance (p=0.445). **B:** The progression free survival rate of patients in IMRT group and VBT group had no statistical significance (p=0.432).

cant differences between the two groups (p>0.05). In terms of long-term adverse reactions, the incidence of radiation cystitis, radiation enterocolitis and radiation colitis in the IMRT group was significantly higher than in the VBT group (p=0.048, p=0.012, p=0.031) (Table 2).

Comparison of quality of life between the two groups of patients before and after treatment

Before treatment, the scores in the FACT-G-V4 scale showed no statistically significant differences between the two groups (p>0.05). After treatment, these scores were evidently decreased in both

Table 4. Univariate analysis of predictors for 5-year progression-free survival rate in patients with endometrial cancer

Parameters	*Total (n=126)* *n (%)*	*5-year PFS* *%*	x^2	*p value*
Age, years			4.253	0.039
<60	73 (53.5)	82.2		
≥60	53 (46.5)	52.8		
Menopause			2.875	0.522
Yes	67 (66.2)	64.2		
No	59 (33.8)	76.3		
Pregnancy history			1.946	0.107
Yes	108 (71.8)	72.2		
No	18 (28.2)	55.6		
Hypertension			0.931	0.890
Yes	39 (71.8)	69.2		
No	87 (28.2)	70.1		
Diabetes mellitus			1.853	0.097
Yes	31 (71.8)	54.8		
No	95 (28.2)	74.7		
Surgical approach			1.646	0.563
A	92 (85.9)	68.5		
B	34 (14.1)	73.5		
Pathological type			1.124	0.090
Endometrioid adenocarcinoma	109 (47.2)	72.5		
Others	17 (35.9)	52.9		
Histological grade			5.167	0.033
G2	72 (7.7)	80.6		
G3	54 (9.2)	55.6		
FIGO stage			5.795	0.027
Ic	91 (28.9)	79.1		
IIa	35 (57.0)	45.7		
Tumor diameter, cm				
<4	37 (71.8)	70.3	0.879	0.794
≥4	89 (28.2)	69.7		
Vascular invasion			3.953	0.044
Yes	97 (71.8)	63.9		
No	29 (28.2)	89.7		
Lower uterine segment invasion			7.690	0.007
Yes	41 (28.2)	43.9		
No	85 (71.8)	82.4		
Anemia before treatment			6.986	0.011
Yes	28 (71.8)	39.3		
No	98 (28.2)	78.6		
Radiotherapy method			1.827	0.432
IMRT	63 (71.8)	73.0		
VBT	63 (28.2)	66.7		

A: total uterine & bilateral adnexectomy+pelvic lymph node dissection or biopsy; B: Total uterine & bilateral adnexectomy+pelvic lymph node dissection or biopsy + Para-aortic lymph node dissection or biopsy; IMRT: intensity modulated radiation therapy; VBT: vaginal brachytherapy; FIGO: International Federation of Gynecology and Obstetrics.

Table 5. Univariate analysis of predictors for overall survival rate in patients with endometrial cancer

Parameters	*Wald value*	*OR*	*95% CI*	*p value*
Age	4.639	2.263	1.393-4.477	0.038
Histological grade	1.494	1.509	0.891-1.860	0.148
FIGO stage	1.941	1.737	0.795-1.991	0.225
Vascular invasion	0.868	1.347	0.913-1.757	0.411
Lower uterine segment invasion	4.729	2.833	1.234-7.339	0.023
Anemia before treatment	3.856	1.792	1.163-3.746	0.040

OR: odds ratios; CI: confidence interval; FIGO: International Federation of Gynecology and Obstetrics.

groups (p<0.05). The scores of physiological status, social/family status, emotional status and functional status in the FACT-G-V4 scale at 3 months after treatment were significantly higher in the VBT group than those in the IMRT group, showing statistically significant differences (p=0.046, p=0.032, p=0.008, p=0.045) (Table 3).

Follow-up results of patient survival

The patients were followed up for 9-60 months until May, 2020. The 3-year OS rate was 95.2% (60/63) and 90.5% (57/63), and the progression-free survival (PFS) rate was 84.1% (53/63) and 79.4% (50/63) in the IMRT group and VBT group, respectively. The 5-year OS and PFS rates were 87.3% (55/63) and 73.0% (46/63) in IMRT group and 82.5% (52/63) and 66.7% (42/63) in VBT group, respectively. Survival curves of the two groups of patients were plotted by Kaplain-Meier method. Log-rank test was conducted, and it was found that the OS and PFS displayed no statistically significantly differences between the two groups of patients (p=0.445, p=0.432) (Figure 1).

Univariate and multivariate analyses of factors affecting tumor progression in patients with endometrial cancer

The factors that may affect tumor progression in patients with early-stage endometrial cancer were incorporated in the univariate analysis, including age, menopause, history of pregnancy, hypertension, diabetes, surgical approach, pathological type, histological grade, FIGO stage, tumor diameter, vascular invasion, lower uterine segment involvement, anemia before treatment, and radiotherapy method. It was discovered that the age, histological grade, FIGO stage, vascular invasion, lower uterine segment involvement, and anemia before treatment were risk factors affecting the tumor progression in patients with endometrial cancer (p<0.05) (Table 4).

The factors with statistically significant differences in univariate analysis were subjected to multivariate analysis, and the results revealed that advanced age, lower uterine segment involvement and anemia before treatment were independent risk factors for tumor progression in patients with endometrial cancer [odds ratio (OR): 2.263, 95% confidence interval (95% CI): 1.393-4.477, p=0.038, OR: 2.833, 95% CI: 1.234-7.339, p=0.023, OR: 1.792, 95% CI: 1.163-3.746, p=0.040] (Table 5).

Discussion

Early-stage endometrial cancer is mainly treated through surgery. Conducting postoperative adjuvant radiotherapy and/or chemotherapy for patients with high risk factors is a consensus [9]. A study showed that the local recurrence rate is 27% in high- and middle-risk patients with high-grade, deep myometrial invasion and/or lymphovascular space invasion [10]. Postoperative radiotherapy alone for high-risk patients is able to reduce the local recurrence (pelvic and vaginal stump), but cannot reduce distant metastasis, so it cannot prolong the OS [11-13]. Studies have manifested that the local recurrence rate in high-risk patients undergoing postoperative chemotherapy alone is higher than that in those treated with radiotherapy, so combined postoperative chemoradiotherapy is necessary for high-risk patients [14,15]. The toxicity of chemoradiotherapy is one of the vital factors limiting its efficacy. The first issue to be considered is the stage at which the concurrent chemoradiotherapy is performed for patients with high-risk endometrial cancer, which remains controversial. A clinical study conducted by Landrum et al [16] reported that concurrent chemoradiotherapy is capable of improving the 2-year DFS of patients with high-risk stage I-IIB endometrial cancer, with tolerable toxicity. Lee et al [17] reviewed and analyzed clinical data and found that compared with radiotherapy alone, concurrent chemoradiotherapy after surgery for stage I-II endometrial cancer leads to obvious hematological toxicity, without significant differences in DFS and 5-year OS. Most

authors believe that concurrent chemoradiotherapy is safe and effective, which is more suitable for the treatment of stage III or above endometrial cancer [18-20].

In this study, patients with high-risk stage Ic-IIa endometrial cancer were enrolled. The results showed that the efficacy of postoperative extrapelvic IMRT+concurrent chemotherapy and VBT+concurrent chemotherapy was comparable in patients with high-risk early-stage endometrial cancer, and the 5-year OS and PFS rates were 87.3% (55/63) and 73.0% (46/63) in the IMRT group and 82.5% (52/63) and 66.7% (42/63) in the VBT group, respectively. Based on the results of log-rank test, there were no statistically significantly differences in the OS and PFS between the two groups of patients (p=0.445, p=0.432).

Since chemoradiotherapy results in toxic reactions, the choice of chemotherapy drugs and specific methods of chemoradiotherapy is particularly important. Wortman proposed in a study that intracavitary radiotherapy is the first-choice adjuvant treatment approach for patients with early-stage endometrial cancer, which results in lower toxicity and better quality of life in contrast with extrapelvic irradiation, so it is even after over 7 years [21]. Barillot studied the effect of postoperative IMRT on acute gastrointestinal toxicity in patients with endometrial cancer and discovered that 39.5% of them had acute urethral injury, and 85% suffered acute injury of the gastrointestinal tract [22]. Chronic radiation enteritis and cystitis are caused by the delay of acute radiation injury, which usually occurs after 3 months of radiotherapy. Radioactive rays cause interstitial fibrosis and local tissue ischemia, leading to chronic inflammation and lumen stenosis, or even ulcers and fistulas in severe cases [23]. In this study, it was found that the incidence rate of acute radiation enterocolitis and radiation colitis and long-term radiation cystitis, were remarkably higher in the IMRT group than in the VBT group (p=0.045, p=0.034, p=0.048, p=0.012, p=0.031). Besides, the quality of life score of patients was significantly higher in the VBT group than in the IMRT group (p<0.05).

In addition, the results of multivariate analysis demonstrated that advanced age, lower uterine segment involvement and anemia before radiotherapy were independent risk factors affecting the PFS of patients. Endometrial cancer can occur at any age. Based on literature reports, elderly patients are more likely to have deep myometrial invasion, high histological grade, and advanced surgicopathological stage. Therefore, advanced age is usually considered as a high-risk factor for endometrial cancer [24]. In addition, patients with lower uterine segment involvement are more prone to lymph node metastasis that results in poor chemotherapy effects, which is a major reason for the poor prognosis of such patients. There are many reports on the effect of anemia during radiotherapy on the efficacy of radiotherapy for various tumors. The results of this study also uncovered that anemia before radiotherapy had an obvious association with the PFS rate of patients. The impact of anemia on the efficacy of tumor therapy is not precisely clear, but it is believed that anemia can cause tumor hypoxia and increase the resistance of tumors to chemoradiotherapy, thereby weakening the treatment efficacy.

There were some shortcomings in this study. For instance, the sample size was limited, the follow-up period was relatively short, and the follow-up content was incomprehensive. Hence, well-designed and reliable prospective clinical studies with a large sample size are needed in the future to support the conclusion made in this study.

Conclusions

Postoperative VBT + concurrent TC chemotherapy has similar effect as postoperative extrapelvic irradiation IMRT+concurrent TC chemotherapy in treating patients with high-risk early-stage endometrial cancer, but patients receiving the former have fewer adverse reactions and high quality of life. Advanced age, lower uterine segment involvement and anemia before treatment are independent risk factors affecting tumor progression in such patients.

Conflict of interests

The authors declare no conflict of interests.

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