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Efficacy and Safety of Image-Guided Intensity-Modulated Radiation Therapy and Volumetric Modulated Arc Therapy Combined with Paclitaxel Liposomes and Cisplatin for Locally Advanced Stage IIB–IIIB Cervical Cancer: A Retrospective Study at a Single Center

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Data Interpretation D
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Background: This retrospective study aimed to investigate the efficacy and safety of image-guided intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) combined with administration of paclitaxel liposomes and cisplatin for locally advanced stage IIB–IIIB cervical cancer at a single center in China.

Material/Methods: The clinical data of 126 patients with stage IIB–IIIB cervical cancer treated in our hospital were retrospectively analyzed. The patients were divided into the IMRT group (n=63) and the VMAT group (n=63). The short-term clinical efficacy, the incidence of adverse reactions, the quality-of-life score, and the changes in levels of T-lymphocyte subsets, serum inflammatory factors, and tumor markers were compared pre- and posttreatment between the 2 groups.

Results: The clinical response rate was 90.5% and 96.8% in the IMRT group and the VMAT group, respectively; the difference was not statistically significant. After treatment, the levels of $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ subsets rose significantly, while the $CD8^+$ level declined significantly in both groups compared with the pretreatment levels. After treatment, the levels of serum vascular endothelial growth factor, squamous cell carcinoma antigen, interleukin-8, tumor necrosis factor-α, carcinoembryonic antigen, and carbohydrate antigen 125 declined in both groups compared with pretreatment levels. After treatment, the Karnofsky performance scale score rose in both groups, and it was higher in the VMAT group than in the IMRT group.

Conclusions: IMRT and VMAT combined with paclitaxel liposomes and cisplatin have similar short-term clinical efficacy and long-term survival rates in the treatment of stage IIB–IIIB cervical cancer.

MeSH Keywords: Cisplatin • Radiotherapy, Intensity-Modulated • Uterine Cervical Neoplasms

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Background

Cervical cancer is the most common gynecological malignancy [1]. Among individuals with this cancer, carcinoma *in situ* is more frequent at 30–35 years of age, while invasive carcinoma often occurs at 45–55 years [1]. In recent years, cervical cancer has become more common among younger people [2]. Concurrent radiochemotherapy is widely recognized as the preferred clinical treatment for patients with mid-stage to advanced cervical cancer [3]. A new type of radiotherapy technique developed and used in recent years is volumetric modulated arc therapy (VMAT) [4]. Compared with traditional intensity-modulated radiation therapy (IMRT) [5,6], VMAT can effectively improve the conformal intensity, reduce the irradiation dose to important organs, and help shorten the treatment time [7,8]. However, it is unknown whether VMAT- or IMRT-based concurrent radiochemotherapy can achieve better clinical benefits for patients with cervical cancer.

Currently, many kinds of chemotherapy, including cisplatin, are available for locally advanced cervical cancer [9]. Paclitaxel is a natural secondary metabolite that can be isolated and purified from the bark of *Taxus chinensis*, and it has been shown to have a good antitumor effect, especially in gastric cancer, ovarian cancer, uterine cancer, and breast cancer with a higher morbidity rate [10–12]. Paclitaxel liposomes, which are used in locally advanced cervical cancer [13], not only increase the water solubility of paclitaxel, but also reduce the incidence rate of allergic reactions, making treatment safer and more reliable [14]. In the present study, the stage of cervical carcinoma was based on the current guidelines for staging cervical carcinoma and patient prognosis [15,16]. This retrospective study aimed to investigate the efficacy and safety of image-guided IMRT and VMAT combined with administration of paclitaxel liposomes and cisplatin for locally advanced stage IIB–IIIB cervical cancer at a single center in China.

Material and Methods

General data

A total of 126 patients with locally advanced (stage IIB–IIIB) cervical cancer treated in our hospital from March 2015 to December 2016 were retrospectively analyzed. The patients were divided into the IMRT group (n=63) and the VMAT group (n=63) based on the type of radiotherapy technique used. Study inclusion criteria for patients were the following: (1) cervical cancer diagnosed via cervical ThinPrep cytologic test and pathological biopsy, (2) stage IIB–IIIB cancer according to the International Federation of Gynecology and Obstetrics 2009 criteria, (3) Karnofsky performance scale (KPS) score ≥70 points, (4) no contraindications for radiochemotherapy, and (5) no radiochemotherapy prior to enrollment. Exclusion criteria were (1) the presence of other malignant tumors; (2) dysfunction of the liver, kidneys, or other important organs; and (3) mental disease or blood system disease. The patients were aged 28.2 to 67.8 years old, with a median age of 53.4 years. The 2 groups had no statistically significant differences at baseline, and they were comparable (P>0.05) (Table 1). All patients were enrolled in accordance with the Declaration of Helsinki and signed informed consent. This study was approved by the Ethics Committee of Chun'an County Traditional Chinese Medicine Hospital.

Treatment methods

In the IMRT group, IMRT was performed in combination with administration of paclitaxel liposomes and cisplatin. Before radiotherapy, the computed tomography machine was used for simulated positioning. Patients were in a supine position with their head on their hands, and the clinical target volume (CTV) was delineated from the superior border of the first lumbar vertebra to the inferior ischial tuberosity at a slice thickness of 5 mm, including primary tumor lesions and paracervical tissues, using the radiotherapy treatment planning system. The pelvic lymphatic drainage region was determined according to the direction of vessels. CTV was expanded outward for 0.5 cm to obtain the planning target volume (PTV), and the PTV was wrapped by a 100% isodose curve. Then, 5-field isocenter irradiation was performed 25 to 28 times using a 6 MV-X linear accelerator (Shandong Shinva Medical Equipment Co., Ltd., Zibo, China, model: XHAl400) (external exposure: 45–50 Gy, 1.8–2 Gy/time). Mono-chemotherapy with paclitaxel liposomes (55 mg/m^2; Nanjing Luye Pharmaceutical Co., Ltd., Nanjing, China, NMPN 2H3030057) was conducted simultaneously. Paclitaxel liposomes were dissolved in a glucose solution and infused intravenously for 3 h. Cisplatin was also intravenously infused (30 mg/m^2) within 30 min, once a week for 5 consecutive times. During a 30-min pretreatment period before intravenous infusion of paclitaxel liposomes, 40 mg of diphenhydramine was injected intramuscularly, 5 mg of dexamethasone was infused intravenously, and 100 mg of cimetidine was injected intravenously.

In the VMAT group, chemotherapy was performed in the same way as in the IMRT group. Computed tomography simulated positioning, treatment planning system for CTV, and irradiation range were also the same as in the IMRT group. The single irradiation dose to PTV was 1.8 Gy for a total of 28 times. Three-dimensional intracavity irradiation was conducted 5 times at an interval of 2 weeks. The volume dose limits for the involved organs were as follows: bladder D2 cm^3 ≤5.5 Gy, and rectum D2 cm^3 ≤5 Gy. The doses of *in vitro* and intracavity irradiation were superimposed according to the equivalent uniform dose criteria. VMAT was used for adjuvant therapy,

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Table 1. Baseline demographic and clinical characteristics of the studied patients.

Parameters	IMRT group (n=63)	VMAT group (n=63)	*P*-value
Age	54.36±10.03	52.91±9.67	0.410
Course of disease (years)	3.2±0.7	3.4±0.8	0.138
Histology			0.528
Squamous cell carcinoma	48 (79.2%)	53 (83.3%)	
Adenocarcinoma	10 (16.7%)	7 (14.6%)	
Adenosquamous carcinoma	5 (4.1%)	3 (2.1%)	
Tumor size (cm)	3.7±1.2	3.5±1.0	0.088
FIGO stage			0.534
II B	22 (18.8%)	28 (22.9%)	
III A	27 (22.9%)	24 (29.2%)	
III B	14 (56.3%)	11 (47.9%)	
Differentiation degree			0.771
High	16 (31.3%)	18 (27.1%)	
Moderate	29 (43.7%)	25 (54.2%)	
Low	18 (25.0%)	20 (18.7%)	
KPS score			0.367
80–90	39 (43.7%)	34 (54.2%)	
70–80	24 (25.0%)	29 (18.7%)	

IMRT –intensity-modulated radiation therapy; VMAT – volumetric modulated arc therapy; FIGO – Federation of Gynecology and Obstretics; KPS – Karnofsky Performance Status.

rotating clockwise at an initial angle of 182° and an end angle of 178°. The dose limit was 0.5 Gy/cm^3 for the small intestine, 0.6 Gy/cm^3 for the rectum, 60 Gy for the bladder, and 50 Gy for the femoral head.

Observation indexes

Short-term efficacy was evaluated at 1 month after treatment based on the Response Evaluation Criteria in Solid Tumors of the World Health Organization [17]. Complete remission (CR) was defined by the complete disappearance of lesions for >4 weeks. For partial remission (PR), the lesions shrank by ≥50% of the basal level for >4 weeks and no new lesions were found. Stable disease (SD) meant that the lesions shrank by <50% of the basal level or expanded by ≤25% of the basal level, and no new lesions were found. In progressive disease (PD), the lesions expanded by >25% of the basal level or there were new lesions.

The toxic and adverse effects of drugs were assessed based on the Radiation Therapy Oncology Group classification criteria for acute radiation injury [18], including radiation proctitis, radiation cystitis, myelosuppression, gastrointestinal reactions, and hepatic-renal dysfunction. Before treatment and at 3 months after treatment, the patient's health status was evaluated using the KPS score; the higher the score, the better the health status. Before and after treatment, peripheral blood was drawn from patients in both groups. The levels of CD3$^+$, CD4$^+$, and CD8$^+$ T lymphocytes were detected using a CytoFLEX Flow Cytometer (Beckman Coulter, Miami, FL, USA), and the CD4$^+$/CD8$^+$ ratio was calculated. In addition, venous blood samples were collected from patients. The levels of serum carcinoembryonic antigen (CEA) and carbohydrate antigen 125 (CA125) were measured using electrochemiluminescence, and the levels of serum tumor necrosis factor (TNF)-α, interleukin (IL)-8, vascular endothelial growth factor (VEGF), and squamous cell carcinoma antigen (SCCA) were determined via double-antibody sandwich enzyme-linked immunoassay.

After treatment, the patients were reexamined in clinic once every 1–2 months for 1 year, once every 3 months in the second year, and once every 3-6 months in the third year and afterward. The survival status of patients was recorded via follow-up until December 2019.

Statistical analysis

Statistical Product and Service Solutions (SPSS) 22.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. Measurement data are expressed as mean±standard deviation, and *t* test was performed for intergroup comparison.

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Table 2. Clinical effective rates of the two studied groups.

Parameters	IMRT group (n=63)	VMAT group (n=63)	*P*-value
CR	34 (54.0%)	41 (65.1%)	
PR	22 (34.9%)	20 (31.7%)	
SD	6 (9.5%)	2 (3.2%)	
PD	0 (0%)	0 (0%)	
ORR	56 (90.5%)	61 (96.8%)	0.144

IMRT – intensity-modulated radiation therapy; VMAT – volumetric modulated arc therapy; CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease; ORR – overall response rate.

Table 3. Comparison of immunological indicators of patients in the two studied groups.

	IMRT group (n=63)	VMAT group (n=63)	*P*-value
$CD3^+$ T cell (%)			
Pretreatment	56.09±8.18	55.38±9.10	0.646
Posttreatment	71.61±13.63	72.72±11.14	0.618
$CD4^+$ T cell (%)			
Pretreatment	35.13±4.09	34.75±4.03	0.600
Posttreatment	47.51±6.47	48.88±6.08	0.223
$CD8^+$ T cell (%)			
Pretreatment	32.12±4.51	31.87±4.69	0.761
Posttreatment	25.61±3.58	24.88±3.90	0.276
$CD4^+/CD8^+$ ratio			
Pretreatment	1.06±0.13	1.03±0.15	0.233
Posttreatment	2.04±0.29	2.08±0.24	0.401

IMRT – intensity-modulated radiation therapy; VMAT – volumetric modulated arc therapy.

Enumeration data are expressed as rate (percentage), and χ^2 test was performed for intergroup comparison. The survival curves were plotted using the Kaplan-Meier method. Log-rank testing was used to detect statistically significant differences in the survival rate between the 2 groups, and $P<0.05$ was considered to be statistically significant.

Results

Comparison of short-term clinical efficacy

The short-term efficacy was observed at 1 month after treatment. The IMRT group had 34 (54.0%) cases of CR, 22 (34.9%) cases of PR, 6 (9.5%) cases of SD, and 0 cases of PD, and the overall response rate was 90.5% (56/63). The VMAT group had 41 (65.1%) cases of CR, 20 (31.7%) cases of PR, 2 (3.2%) cases of SD, and 0 cases of PD, and the overall response rate was 96.8% (61/63). There was no statistically significant difference in the short-term overall clinical response rate between the 2 groups ($P=0.144$; Table 2).

Comparisons of T-lymphocyte subsets levels before and after treatment

Before treatment, no statistically significant differences were found in $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ levels between the 2 groups ($P>0.05$). After treatment, $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ levels rose significantly and the level of $CD8^+$ declined significantly in both groups compared with the levels before treatment ($P<0.05$). After treatment, $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ levels had no statistically significant differences between the 2 groups ($P>0.05$; Table 3).

Comparisons of serum indexes before and after treatment

Before treatment, the 2 groups had no statistically significant differences with regard to serum levels of VEGF, SCCA, IL-8,

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Table 4. Comparison of preoperative and postoperative serum inflammatory factors and tumor markers of patients in the two studied groups.

	IMRT group (n=63)	VMAT group (n=63)	*P*-value
VEGF (pg/mL)			
Preoperative	202.23±70.84	206.48±73.78	0.742
Postoperative	86.14±19.09	78.62±16.14	0.019
SCCA (mg/L)			
Preoperative	7.51±1.19	7.69±1.43	0.444
Postoperative	4.42±0.63	3.83±0.72	0.001
IL-8 (pg/mL)			
Preoperative	0.24±0.18	0.21±0.17	0.338
Postoperative	0.14±0.09	0.10±0.07	0.006
TNF-α (pg/mL)			
Preoperative	2.82±0.78	2.69±0.70	0.327
Postoperative	1.18±0.32	1.04±0.26	0.008
CEA (μg/L)			
Preoperative	21.89±4.13	22.37±4.26	0.522
Postoperative	9.61±1.14	9.04±1.45	0.016
CA125 (U/mL)			
Preoperative	45.27±5.63	44.72±5.60	0.584
Postoperative	24.47±4.51	22.68±4.38	0.026

IMRT – intensity-modulated radiation therapy; VMAT – volumetric modulated arc therapy; VEGF – vascular endothelial growth factor; SCCA – squamous cell carcinoma antigen; IL – interleukin; TNF – tumor necrosis factor; CEA – carcino-embryonic antigen; CA – carbohydrate antigen.

TNF-α, CEA, and CA125 ($P>0.05$). After treatment, the serum levels of VEGF, SCCA, IL-8, TNF-α, CEA, and CA125 declined in both groups compared with the levels before treatment. In addition, they were significantly lower in the VMAT group than in the IMRT group ($P=0.019$, $P<0.001$, $P=0.006$, $P=0.008$, $P=0.016$, and $P=0.026$, respectively; Table 4).

Comparison of quality of life before and after treatment

The KPS score was not statistically different between the IMRT group and the VMAT group before treatment (75.8±6.9 points *vs.* 76.5±7.7 points; $P=0.592$). After treatment, the KPS score rose in both groups and was significantly higher in the VMAT group than in the IMRT group (83.2±8.9 points *vs.* 79.4±8.8 points; $P=0.017$).

Comparison of incidence of adverse reactions

The treatment-related adverse reactions mainly included myelosuppression, allergic reactions, gastrointestinal reactions, muscle and joint pain, alopecia, hepatic-renal dysfunction, radiodermatitis, radiation cystitis, and radiation proctitis, mostly in grades I–II. All adverse reactions improved after symptomatic treatment, without affecting treatment. The incidence rate of myelosuppression was markedly lower in the VMAT group than that in the IMRT group (44.4% *vs.* 71.4%, $P=0.003$), and the incidence rate of grade III–IV myelosuppression was 11.1% (7/63) and 19.0% (12/63), respectively, in the 2 groups. No statistically significant difference was found in the incidence rate of other adverse reactions between the 2 groups ($P>0.05$). In the IMRT group and the VMAT group, the incidence rate of grade III–IV gastrointestinal reactions was 6.3% (4/63) and 4.8% (3/63), that of grade III–IV alopecia was 3.2% (2/63), that of grade III–IV radiation cystitis was 1.6% (1/63), and that of grade III–IV radiation proctitis was 3.2% (2/63) and 1.6% (1/63), respectively (Table 5).

Follow-up results of patients' survival status

As of December 2019, a total of 126 patients were followed in the 2 groups, with a median follow-up time of 28.9 months (6-36 months). In the IMRT group and the VMAT group, the 1-year overall survival (OS) rate was 90.5% (57/63) and 95.2% (60/63), and the 3-year OS rate was 71.4% (45/63) and 79.4% (50/63),

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Table 5. Comparison of complications of the studied patients in two groups.

Parameters	IMRT group (n=63)		VMAT group (n=63)		*P*-value
	Grade I–II	Grade III–IV	Grade I–II	Grade III–IV	
Myelosuppression	33 (52.4%)	12 (19.0%)	21 (33.3%)	7 (11.1%)	0.003
Allergic reaction	11 (17.5%)	0 (0.0%)	5 (7.9%)	0 (0.0%)	0.108
Gastrointestinal reaction	41 (65.1%)	4 (6.3%)	44 (69.8%)	3 (4.8%)	0.688
Muscle & joint pain	25 (39.7%)	0 (0.0%)	20 (31.7%)	0 (0.0%)	0.353
Alopecia	42 (66.7%)	2 (3.2%)	36 (57.1%)	2 (3.2%)	0.262
Hepatic function damage	10 (15.9%)	0 (0.0%)	8 (12.7%)	0 (0.0%)	0.611
Renal function damage	7 (11.1%)	0 (0.0%)	9 (14.3%)	0 (0.0%)	0.593
Radiodermatitis	19 (30.2%)	0 (0.0%)	16 (25.4%)	0 (0.0%)	0.551
Radiocystitis	22 (34.9%)	1 (1.6%)	24 (38.1%)	1 (1.6%)	0.714
Radioproctitis	38 (60.3%)	2 (3.2%)	35 (55.6%)	1 (1.6%)	0.466

IMRT – intensity-modulated radiation therapy; VMAT :– volumetric modulated arc therapy.

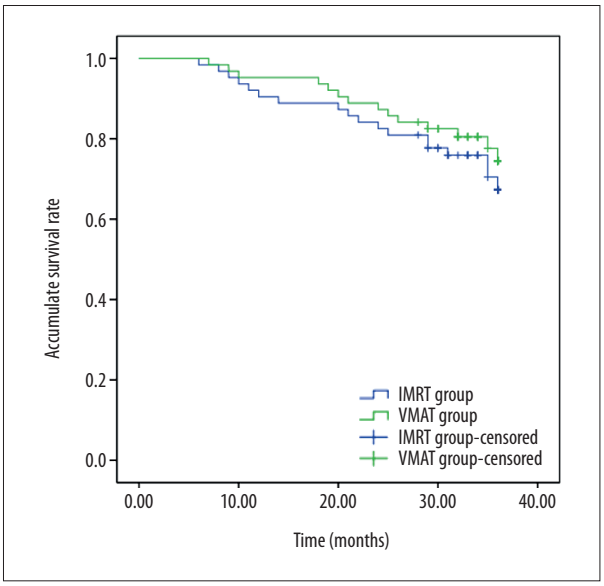

Figure 1. Kaplan-Meier survival curves of patients in the IMRT group and the VMAT group. The difference in overall survival rates between groups was not statistically significant (*P*=0.416). IMRT – intensity-modulated radiation therapy; VMAT – volumetric modulated arc therapy.

respectively. The Kaplan-Meier survival curves are shown in Figure 1. The results of the log-rank test showed that the difference in the OS rate between the 2 groups was not statistically significant (*P*=0.416).

Discussion

Our study investigated the efficacy and safety of image-guided IMRT and VMAT combined with administration of paclitaxel liposomes and cisplatin for locally advanced stage IIB–IIIB cervical cancer at a single center in China. Currently, radiotherapy is the main treatment for cervical cancer and one of the most effective, with about 80–85% of patients undergoing radiotherapy to reduce the risk of metastasis and recurrence [19]. In recent years, studies have found that the range of hypoxia in cancer cells is significantly broader in patients with mid-stage to advanced cervical cancer, and their sensitivity to radiotherapy declines. Therefore, concurrent radiochemotherapy has gradually become the main therapeutic regimen for patients with mid-stage to advanced cervical cancer [20]. Paclitaxel liposomes are cytotoxic antitumor drugs that promote the assembly of microtubule dimers and inhibit their disaggregation, hindering cell division and thereby suppressing the growth of cancer cells. Paclitaxel liposomes are water soluble, which increases the proportion of drug that is distributed in the reticuloendothelial system, thereby prolonging the retention time of an effective blood drug concentration and enhancing the anticancer effect [21]. In this study, the short-term efficacy had no statistically significant difference between the IMRT group and the VMAT group (90.5% *vs.* 96.8%). The long-term follow-up results showed no statistically significant difference in the OS rate between the 2 groups (*P*=0.416). IMRT and VMAT combined with paclitaxel liposomes were found to have similar efficacy in patients with mid-stage to advanced cervical cancer.

VMAT is a new type of radiotherapy technique that adopts a single arc or multiple arcs to optimize the rotation angle of the gantry, adjust the raster shape, and improve the output

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dose rate, thereby modulating the intensity of the target region. During VMAT, a beam of rays is continuously emitted, and equipment movement speed, irradiation dose rate, irradiation field shape, and angle are dynamically adjusted, making the conformal dose distribution better than that of traditional IMRT [22]. According to the dosimetry research, VMAT is similar to IMRT in terms of the radiation uniformity, conformity, and surrounding tissue dose in the PTV, but the application time of VMAT is shorter, which improves the radiation safety for important organs [22]. The irradiation dose from VMAT for the small intestine V20, rectum V30 and V45, and femoral head V20 and V30 have been verified to be lower than those of IMRT [23]. Other research has shown that the dose requirements of all PTV and the dose distribution of CTV are relatively similar between VMAT and IMRT, but VMAT is superior in the dose distribution of the vital organs at risk [24]. In the current study, the KPS score rose after treatment in both groups and was significantly higher in the VMAT group, indicating that the patients had better functional status. In terms of adverse reactions, the incidence rate of myelosuppression was markedly lower in the VMAT group than in the IMRT group (44.4% *vs.* 71.4%, P=0.003). No statistically significant difference was found in the incidence rate of other adverse reactions between the 2 groups (P>0.05).

T lymphocytes are one of the most important cell populations in the immune system, and they are related to the normal immune function of the body. In the current study, we found that the levels of serum $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ rose significantly after treatment, while the level of $CD8^+$ declined significantly in both groups compared with the levels before treatment. The above indexes were not statistically significantly different between the 2 groups after treatment (P>0.05). Radiotherapy exerts an inhibitory effect on T lymphocytes in patients. However, paclitaxel liposomes have a targeting ability that enables them to release the drugs directly into the tumor and induce antitumor immunity in the body after tumor cells are engulfed by phagocytes, thus avoiding damage to T-lymphocyte subsets.

VEGF plays an important role in tumor angiogenesis, growth, and metastasis. High expression of VEGF indicates a poor prognosis, and VEGF-targeted therapy for cancer is currently a hotspot in drug research [25,26]. SCCA is a commonly used serum tumor marker for cervical cancer, and detecting its level in serum is valuable for the diagnosis of tumors and evaluation of prognosis [27,28]. CEA is a type of tumor cell surface antigen, and it is often used for the clinical detection of digestive system cancer and has recently also been used as an auxiliary diagnostic index for cervical cancer, breast cancer, and other gynecological cancers. CA125 is a protein antigen, and its level rises in about 75% of patients with cervical cancer [29]. In the current study, the serum levels of VEGF, SCCA, IL-8, TNF-α, CEA, and CA125 were found to decline markedly after treatment, and they were notably lower in the VMAT group than in the IMRT group. In mice with lung cancer, paclitaxel reduced the level of serum VEGF through inhibiting tumor angiogenesis and blocking hypoxia-induced angiogenesis [26]. In addition, paclitaxel can inhibit tubulin polymerization, block mitosis, and inhibit differentiation in tumor cells, thereby lowering the level of serum SCCA.

This study was a retrospective study, so data bias was likely. Further, the sample size was small and the follow-up period was short. Therefore, our conclusions need to be verified in prospective multi-center randomized controlled trials to provide a reliable basis for the treatment of locally advanced cervical cancer.

Conclusions

The findings from this retrospective study at a single center in China on the efficacy and safety of image-guided IMRT and VMAT combined with the administration of paclitaxel liposomes and cisplatin showed similar short-term clinical efficacy and long-term survival rate in locally advanced stage IIB–IIIB cervical cancer. However, compared with IMRT, VMAT significantly lowered the incidence rate of myelosuppression, reduced the levels of serum tumor markers and inflammatory factors, and improved the quality of life of patients.

Conflict of interest

None.

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