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Evaluation of the toxicity of prophylactic extended-field radiation therapy with volumetric modulated arc therapy in combination with concomitant chemoradiotherapy in patients with locally advanced stage IIIC1r cervical cancer according to the 2018 FIGO classification

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ABSTRACT

Background: To evaluate the toxicity of prophylactic extended-field radiation therapy (EFRT) combined with volumetric modulated arc therapy (VMAT) in combination with cisplatin chemotherapy for locally advanced stage IIIC1r cervical cancer [2018 International Federation of Gynecology and Obstetrics (FIGO)].

Materials and methods: Thirty patients with stage IIIC1r cervical cancer were treated with EFRT combined with concurrent cisplatin. Acute toxicities were evaluated according to the common terminology criteria for adverse events (CTCAE v.5). Delayed toxicities were evaluated according to the classification criteria of radiation damage toxicity of the Radiation Therapy Oncology Group (RTOG). The efficacy of the regimens was evaluated using response evaluation criteria in solid tumors (RECIST v1.1). Spearman correlation was used to analyze the correlation between acute gastrointestinal toxicity (nausea) and the small bowel V45. Predictive value analysis was performed using a receiver operating characteristic (ROC) curve.

Results: There were no grade ≥ 3 acute toxicities. The most common acute toxicity observed was nausea (grade 2 in 40%), which was positively correlated with the volume of the small intestine receiving 45 Gy. When the V45 of the small intestine was > 83.2 cc, the risk of grade 2 acute upper digestive tract toxicity (nausea) increased. The major late toxicities had the following distributions: Grade 1 diarrhea, 36.7%; Grade 1 abdominal pain, 13.3%; and Grade 1 radiation cystitis. No grade ≥ 2 late toxicities were observed.

Conclusions: Treatment of locally advanced stage IIIC1r cervical cancer with EFRT combined with VMAT and concurrent cisplatin chemotherapy was well tolerated, and the acute toxicity profile was acceptable. Significant grade 3 acute/delayed toxicities were not observed.

Key words: FIGO IIIC1r cervical cancer; extended-field radiation therapy; volumetric modulated arc therapy; toxicity

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Introduction

Globally, cervical cancer ranks as the fourth most common and deadly gynecological malignancy and poses a significant threat to women's health [1]. Radical pelvic concurrent chemoradiotherapy plus brachytherapy is the standard treatment approach for locally advanced cervical cancer [2]. Lymph node metastasis is the most common route of cervical cancer spread. Among these complications, para-aortic lymph node metastasis is one of the common causes of treatment failure after chemoradiotherapy. Pelvic lymph node metastasis is an important predictive factor for para-aortic lymph node recurrence [3]. Prophylactic extended-field radiation therapy (EFRT) is recommended for locally advanced cervical cancer patients with iliac or para-aortic lymph node metastasis. However, there is controversy regarding the use of EFRT in patients with high-risk factors for PALM [4]. Studies have shown that EFRT can effectively reduce the risk of para-aortic lymph node recurrence and distant metastasis in patients with locally advanced cervical cancer with pelvic lymph node metastasis [5].

In recent years, with the rapid development of precise radiotherapy techniques, particularly the widespread application of volumetric modulated arc therapy (VMAT), there has been a significant improvement in dose uniformity and conformity within the tumor target area while effectively protecting normal organs [6]. Currently, there are limited studies reporting on the acute and late toxicities of prophylactic EFRT combined with VMAT in patients with locally advanced cervical cancer. The purpose of this study was to evaluate the acute and late toxicities of EFRT in patients receiving concurrent cisplatin chemotherapy who have International Federation of Gynecology and Obstetrics (FIGO) 2018 stage IIIC1r locally advanced cervical cancer with bilateral pelvic lymph node metastasis and negative iliac and para-aortic lymph nodes.

Materials and methods

General information

A total of 30 patients with locally advanced cervical cancer who received EFRT with VMAT at Beijing Obstetrics and Gynecology Hospital, Capital Medical University, from January 2020 to December 2021 were selected for the study. The follow-up data were complete, and the patients' age ranged from 30 to 65 years, with a median age of 50 years. The study protocol was approved by the ethics committee of the Beijing Obstetrics and Gynecology Hospital, Capital Medical University and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. Informed consent forms were signed by all the patients who accepted the above treatment.

Inclusion and exclusion criteria

The inclusion criteria were as follows:

- age ≤ 70 years and Karnofsky Performance Scale (KPS) > 80 points;
- all patients were histopathologically confirmed by tissue biopsy;
- stage IIIC1r according to the FIGO 2018 staging criteria [7] and based on imaging examinations such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)/CT;
- bilateral pelvic lymph node metastasis was defined as a short-axis diameter ≥ 1.0 cm on CT/MRI or a short-axis diameter < 1.0 cm but > 0.8 cm with lymph nodes located in high-risk regions for metastasis
- patients with no evidence of para-aortic lymph node or distant metastasis on imaging (such as lung, liver, or bone).

The exclusion criteria were as follows:

- severe comorbidities in the internal or surgical field;
- history of previous abdominal or pelvic radiotherapy;
- concurrent malignancies at other sites.

Regarding quality assurance of this study, cervical local biopsies were performed by clinical specialists, the pathological slides were reviewed by the chief physician/associate chief physician of the pathology department, and immunohistochemistry was verified. In cases where there were doubts about the pathological diagnosis, pathological peer review and consultation were conducted to ensure the quality of the pathology. Regarding quality assurance for CT/MR/PET-CT imaging, interpretation of the results was performed by two chief physicians/associate chief physicians, and the maximum short-axis diameter of the lymph

node perpendicular to the vessel was measured in three dimensions to ensure the quality of the imaging interpretation.

External beam radiation therapy

All patients were instructed to drink 800 mL water mixed with 20 ml of iodine-containing oral contrast after fully emptying their bladder and rectum 1 hour before CT positioning. Patients were placed in the supine position on the treatment couch and immobilized using a thermoplastic mask. The center position of the body membrane marker was determined, and a plain-slice scan was performed using a Philips BrillianceTM 16-slice large-aperture CT simulator. The scan range extended from the level of the diaphragm to the upper one-third of the femur, with a slice thickness of 5 mm. The localization images were transferred to the treatment planning system (Eclipse Version 10.0, Varian, USA).

The target volumes and organs at risk (OARs) were defined in accordance with the 2021 RTOG cervical cancer contouring guidelines [8]. The gross tumor volume (GTVnd) was defined as the number of pelvic metastatic lymph nodes (MLNs). The clinical target volume (CTV) included the gross tumor, gross tumor volume (GTVnd), cervix, uterus, parametrium, upper part of the vagina, and pelvic lymph node drainage regions (including the internal iliac, external iliac, obturator, presacral, common iliac, and para-aortic regions). The upper boundary of the CTV was at the level of the renal vessel, and the lower boundary was determined based on the extent of vaginal invasion. The pelvic lymph node drainage regions extended 0.7–1.0 cm beyond the vascular edge. The para-aortic CTV extended 1.0–1.5 cm above the left renal vein, reached the level of the bifurcation of the abdominal aorta as the lower boundary, extended 3–5 mm anterior to the inferior vena cava and 7 mm anterior to the abdominal aorta, and extended 1.0–2.0 cm to the left of the abdominal aorta and 3–5 mm to the right of the inferior vena cava (see Fig. 1). The GTVnd was expanded by 3–5 mm to create the planning GTVnd (PGTVnd). The planning target volume (PTV) included a 10 mm margin in the superior and inferior directions, a 5 mm margin in the left and right directions, a 5–10 mm margin in the anterior direction, and a 7 mm margin in the posterior direction from the CTV. OARs were defined according to ICRU Report 83 [8] and included

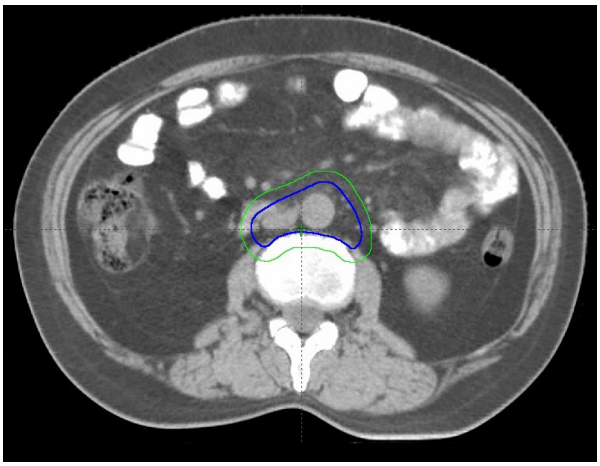

Figure 1. The transverse slice shows the delineation of the clinical target volume (CTV) for prophylactic para-aortic CTVs (blue); there should not be concavity to the contour in the space between the aorta and the inferior vena cava to assure coverage of the interaortocaval nodes; the PTV (green) of the para-aortic target area is also shown

the bladder, rectum, sigmoid colon, small intestine, kidneys, liver, pelvic bones, femoral heads, and spinal cord within a 2.0 cm range above and below the PTV. The planning dose-volume constraints for the PTV and OARs are shown in Table 1. VMAT plans for nonbone marrow-sparing patients were generated on the eclipse planning system. After the completion of the plan, the plan was reviewed and approved by the same chief physician. After dose verification, the treatment images and information were transmitted to the Varian accelerator and its imaging system, kilovolt cone beam CT (CBCT), for radiotherapy.

Concurrent chemoradiotherapy and CBCT verification

Before each radiation treatment, the rectum was emptied. The bladder was emptied, and the patient drank 800 mL of warm water 1 hour before radiation treatment. Treatment was administered when the sensation of holding urine matched the sensation during the CT scan. CBCT position verification was performed for the first 5 fractions and then once a week. All patients received concurrent chemotherapy with cisplatin (40 mg/m^2 per week). Chemotherapy was temporarily suspended if the white blood cell (WBC) count was less than 3.0×10^9/L or the platelet count (PLT) was less than 100×10^9/L, and leukocyte or platelet support therapy was given.

Table 1. Planning dose-volume constraints

Structure	Planning constraints
PGTVnd	At least 95% PGTVnd to receive 100% of prescription dose (59.92 Gy/2.14 Gy/28 f)
PTV	At least 95% PTV to receive 100% of prescription dose (50.4 Gy/1.8 Gy/28 f)
Rectum	V45 < 50%
Bladder	V45 < 50%
Small bowel	V20 < 50%, V30 < 40%, D1 cc ≤ 54 Gy
Sigmoid	V45 < 50%, D0.1 cc ≤ 57 Gy
Duodenum	D0.1 cc ≤ 54Gy
Bilateral kidneys	V18 < 33%
Liver	V10 < 33%
Pelvic	V20 < 75%
Femoral heads	V50 < 5%
Spinal cord	D0.1 cc ≤ 40 Gy

PTV — planning target volume

Intracavitary brachytherapy

After external beam radiation therapy (EBRT), image-guided three-dimensional brachytherapy (IGBT) was performed twice a week using a high dose ratio (HDR) of 192Ir, with 30 to 36 Gy in 5 to 6 fractions to point A.

Adverse reaction evaluation

During EBRT, complete blood counts and renal function were evaluated weekly for all patients. Acute toxicity was defined as radiation reactions occurring within 1 to 90 days of radiation treatment and was assessed using the Common Terminology Criteria for Adverse Events (CTCAE 5.0) [9]. The severity of late toxicity was classified following the late radiation injury grading criteria developed by the Radiation Therapy Oncology Group (RTOG) [10].

Short-term efficacy evaluation and follow-up

The first follow-up occurred at 6 weeks after the completion of external beam radiotherapy and brachytherapy and included gynecological examination, assessment of toxic reactions, abdominal and pelvic CT, and pelvic MRI for evaluating treatment efficacy. If a complete response (CR) was achieved, subsequent follow-up visits were scheduled every 3 months. After the treatment was complete, PET-CT was repeated 6 months later to determine whether the treatment had been successful. The follow-up period extended until December 2023. Efficacy assessment was based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [11].

Statistical analysis

Patient characteristics, such as age, stage, histological type, tumor size, lymph node size and number, acute and late toxicities, and dose parameters, were analyzed using SPSS 19.0 software. Descriptive statistics were used to summarize the parameters and their frequency distributions. The primary endpoint of the study was evaluation of acute and late toxicities of EFRT. The secondary endpoint was observation of the correlation between acute gastrointestinal toxicity (nausea) and the volume of the small intestine receiving 45 Gy, which was analyzed using the Spearman correlation coefficient. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value of the signature. A p value of less than 0.05 was considered indicative of statistical significance.

Results

Clinical characteristics of patients

Descriptive statistical methods were used to evaluate the clinical and pathological characteristics as shown in Table 2. The median duration of

Table 2. Baseline and lymph node characteristics

Characteristics	Proportion (n)
Median age (years, range)	50 (30–65)
Median KPS score (range)	90 (80–90)
Histological type	
Squamous cell carcinoma	93.3% (28/30)
Nonsquamous cell carcinoma	6.7% (2/30)
Median primary tumor diameter [cm, range]	5.1 (2.5–7.0)
Lymph node metastasis site	
Simple bilateral external iliac	80% (24/30)
Bilateral external iliac plus internal iliac	20% (6/30)
Number of lymph node metastases (range)	3 (2–6)
Median size of the largest lymph nodes (cm, range)	1.2 (0.8–2.8)
Median maximum SUV value of lymph nodes (range)	8.6 (2.6–36.1)
Total number of lymph nodes given SIB	85

KPS — Karnofsky Performance Status; SUV — standard uptake value; SIB — simultaneous integrated boost

Table 3. Dosimetric parameters for planning gross tumor volume (PGTVnd), planning target volume (PTV), and organs at risk (OARs)

Dosimetric parameters	Median values
PTV volume	1570.1 cc
PTV D2	118.6%
PTV D50	104.4%
PTV D98	99%
PGTVnd volume	27.8 cc
PGTVnd D2	105.8%
PGTVnd D50	102.9%
PGTVnd D98	99.2%
Small bowel V45	77.7 cc
Rectum Dmax	54.8 Gy
Bladder Dmax	61.3 Gy
Kidneys Dmean	12.6 Gy
Femoral heads Dmax	49.7 Gy
Spinal cord Dmax	36.7 Gy

EBRT completion was 5.6 weeks (range: 5.3-6.6 weeks). The median overall treatment completion time was 9.1 weeks (range: 7.8–11.9 weeks). The median number of cycles of concurrent cisplatin chemotherapy was 5 (range: 3–6 cycles). There were no prolonged interruptions in external beam radiation therapy due to acute toxic reactions.

Dosimetric analysis

The median volume of the PTV was 1570.1 cc (range: 1242.5–2054 cc). Dosimetric parameters for PGTVnd, PTV, and OARs were obtained based on the dose-volume histogram (DVH), as shown in Table 3. An example of the dose distribution profile for the PTV in the EFRT plan for cervical cancer is shown in Figure 2.

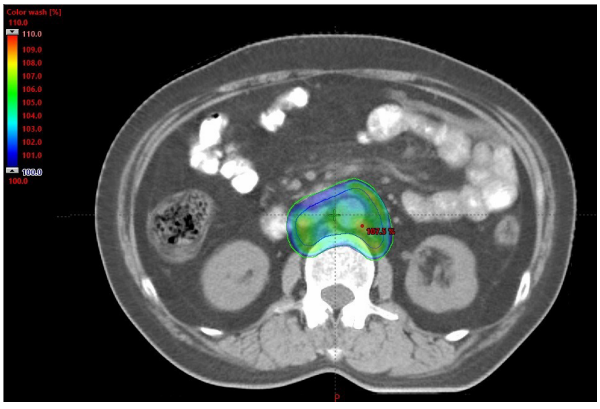

Figure 2. An example of the dose distribution profile for the planning target volume (PTV) of the para-aortic target area The dose-color wash indicates doses between 50.4 Gy (100%) and 55.4 Gy (110%)

Acute toxicity evaluation

Acute toxicities were evaluated weekly from the start of EBRT until the completion of intracavitary irradiation, and the highest grade of toxicity reaction was recorded (Tab. 4). The majority of patients receiving VMAT in the EFRT experienced grade 1 or 2 acute toxicity, indicating good overall

Table 4. Acute toxicity profile

Acute toxicity	Grade	Proportion (n)
Systematic symptoms		
Fatigue	0	16.7% (5/30)
	1	80% (24/30)
	2	3.3% (1/30)
Fever	0	93.3% (28/30)
	1	6.7% (2/30)
	2	0
Weight loss	0	76.7% (23/30)
	1	23.3% (7/30)
	2	0
Hematologic		
Anemia	0	36.7% (11/30)
	1	40.0% (12/30)
	2	23.3% (7/30)
Leucopenia	0	33.3% (10/30)
	1	26.7% (8/30)
	2	40.0% (12/30)
Thrombocytopenia	0	80.0% (24/30)
	1	13.3% (4/30)
	2	16.7% (2/30)
Gastrointestinal		
Nausea	0	26.7% (8/30)
	1	40.0% (12/30)
	2	33.3% (10/30)
Vomiting	0	86.7% (26/30)
	1	13.3% (4/30)
	2	0
Diarrhea	0	43.3% (13/30)
	1	33.4% (10/30)
	2	23.3% (7/30)
Radiation cystitis	0	93.3% (28/30)
	1	6.7% (2/30)
	2	0

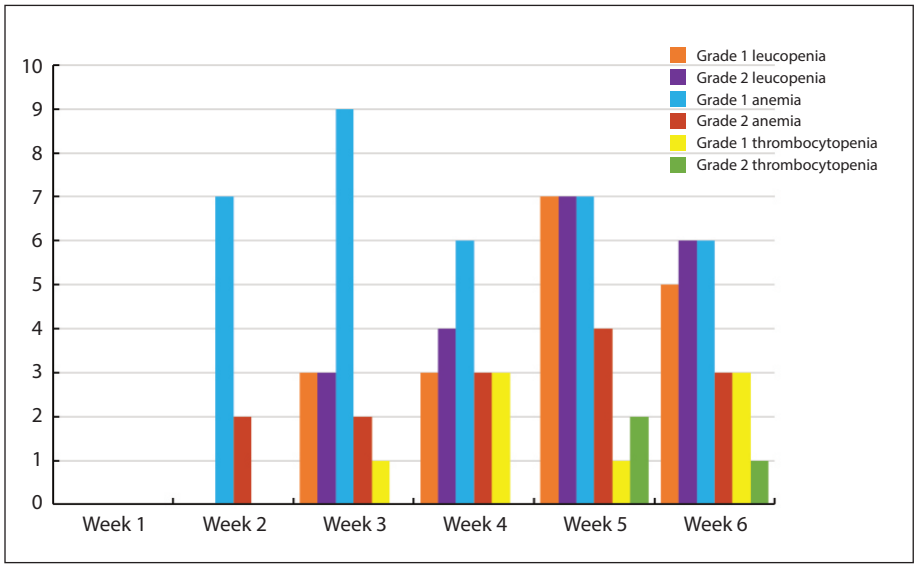

Figure 3. Distribution of acute hematological toxicity events during external beam radiation therapy (EBRT) over time

tolerability. No grade 3 or higher hematological toxicities, such as anemia, leukopenia, or thrombocytopenia, were observed. However, in 8 patients, concurrent chemotherapy was delayed due to grade 2 leukopenia (26.7%). Hematological toxicity increased with the duration of EBRT as shown in Figure 3. The median time for Grade ≥ 2 leukopenia was week 4, and for Grade ≥ 2 anemia, it was week 5. The severity of acute upper gastrointestinal toxicity (nausea) increased with increasing small bowel V45 ($r = 0.769$, $p = 0.001$). Figure 4 presents the ROC analysis of the correlation between small bowel V45 and the occurrence of Grade 2 acute upper gastrointestinal toxicity (nausea), with a predictive sensitivity of 83.3%, specificity of 75%, and a cutoff value for small bowel V45 of 83.2 cc. The degree of acute toxicity did not increase with simultaneous integrated boost (SIB) to the pelvic lymph nodes.

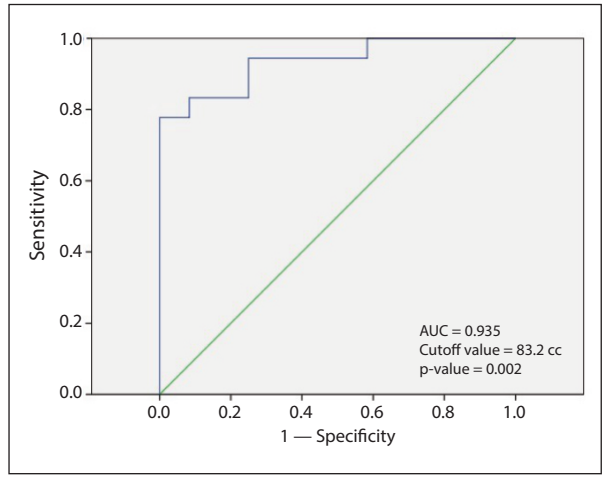

Figure 4. Receiver operating characteristic curve (ROC) analysis of the correlation between small bowel V45 and grade 2 nausea. AUC — area under the curve

Late toxicities and short-term clinical efficacy evaluation

The median follow-up time was 32 months (range 8–46 months). The major late toxicities observed were Grade 1 diarrhea in 36.7% (11/30) of patients, Grade 1 abdominal pain in 13.3% (4/30) of patients, and Grade 1 radiation cystitis in 6.7% (2/30) of patients. No grade ≥ 2 late toxicities were observed.

The initial follow-up results showed a clinical complete response rate of 93.3% (28/30). Follow-up PET-CT at six months revealed one patient with persistent local disease and one patient with pelvic residual nodal disease. As of the median follow-up, 29 patients were alive, 26 had CR, 2 had cervical local disease, 1 had pelvic nodal disease, and 1 had distant metastases (para-aortic and supraclavicular lymph node metastasis). Patients with isolated para-aortic lymph node recurrence were not observed. The median time to recurrence was 13 months (4–30 months).

Discussion

For many years, the potential benefits of prophylactic EFRT in locally advanced cervical can-

cer have been explored. Studies have shown that pelvic lymph node metastasis is an important independent risk factor for PALM [12]. Multiple studies have demonstrated that FIGO stage III–IVA, SCC > 40 μg/L, parametrial involvement, and positive pelvic lymph nodes are independent risk factors for para-aortic lymph node recurrence and metastasis after pelvic radiotherapy [13–15]. Wang et al. conducted a retrospective analysis of clinical data from 778 cervical cancer patients with positive pelvic lymph nodes but negative para-aortic lymph nodes. Among them, 154 patients received prophylactic EFRT, 624 patients received pelvic radiation therapy, and 83% received concurrent chemoradiotherapy. Multivariate analysis revealed that EFRT was an independent risk factor for para-aortic lymph node recurrence and distant metastasis but not for overall survival or disease-free survival. According to the propensity score matching analysis, compared to pelvic radiation therapy, EFRT significantly reduced the rates of distant metastasis (7.0% *vs*. 21.7%, p = 0.016) and para-aortic lymph node recurrence (0% *vs*. 6.6%, p = 0.014) [16]. Lee et al. analyzed 206 patients with FIGO stage IB2-IVA cervical cancer and negative para-aortic lymph nodes. Among them, 110 patients underwent pelvic radiation therapy, and 96 patients underwent EFRT (with the upper border of the target volume at the level of the left renal vein). Among the patients, 20 (18.2%) in the pelvic radiation therapy group and 12 (12.5%) in the EFRT group did not complete concurrent chemotherapy. The results showed that the 5-year para-aortic lymph node recurrence-free survival rates were 87.6% and 97.9% (p = 0.03), and the 5-year overall survival rates were 74.5% and 87.8% (p = 0.04) for the pelvic radiation therapy and EFRT groups, respectively. These studies suggest that EFRT could improve the clinical prognosis of patients with locally advanced cervical cancer.

In our cohort, local sites were the most common sites at which surgery failed (2/30). There was 96.7% control of the paraaortic lymph nodes. The clinical efficacy of this treatment showed that EFRT might reduce the risk of PALN recurrence to some extent in patients with stage IIIC1r locally advanced cervical cancer and bilateral pelvic lymph node metastasis but not in patients with negative iliac or para-aortic lymph node involvement (no PALN recurrence was observed). The possible reasons for the persistent local disease in one patient in our study might include (1) the pathological type being adenocarcinoma, which was insensitive to radiation therapy; (2) the large tumor volume; and (3) severe parametrial involvement.

EFRT techniques evolved from 2D conformal radiation therapy in the early 1990s to modern intensity-modulated radiation therapy (IMRT), especially with the widespread application of VMAT. VMAT significantly reduces the incidence of Grade ≥ 3 acute toxicity in patients after EFRT [18]. Compared to conventional radiation therapy techniques, VMAT improves target dose homogeneity and conformity while effectively reducing the mean dose and high-dose volume to organs at risk. According to the RTOG 0116 study [19], EFRT combined with concurrent cisplatin chemotherapy and conventional radiation therapy resulted in a high incidence of grade III-IV acute toxicities (81%) and grade III–IV late radiation toxicities (40%). A meta-analysis of six studies included a total of 1,008 cervical cancer patients treated with curative radiation therapy, including 350 patients who received intensity-modulated radiation therapy and 658 patients who received 2D or 3D conformal radiation therapy. The results showed no significant difference in 3-year overall survival or disease-free survival between the two groups. However, intensity-modulated radiation therapy significantly reduced the incidence of Grade ≥ 3 acute gastrointestinal toxicity [odds ratio (OR) = 0.55, 95% confidence interval (CI): 0.32–0.95; p = 0.03), Grade ≥ 3 acute genitourinary toxicity (OR = 0.31, 95% CI: 0.14–0.67; p = 0.003), and Grade ≥ 3 chronic genitourinary toxicity (OR = 0.09, 95% CI: 0.01–0.67; p = 0.02) [20]. The 2020 ASTRO clinical practice guidelines recommend the use of intensity-modulated radiation therapy for curative treatment of locally advanced cervical cancer to reduce acute and chronic toxicities [21]. In this study, the VMAT technique was used to minimize radiation toxicity. The results showed that the most common adverse reactions were Grade ≤ 2 acute toxicities (leukopenia, nausea, vomiting, diarrhea, and urinary frequency) and Grade 1 late toxicities (diarrhea, abdominal pain, and radiation cystitis). No grade ≥ 3 acute toxicities or grade ≥ 2 late toxicities were observed.

The severity of acute gastrointestinal toxicity (nausea) was positively correlated with

the volume of the small bowel affected by a dose of V45Gy (V45). A small bowel V45 > 83.2 cc was an independent risk factor for Grade 2 acute upper gastrointestinal toxicity (nausea), with a sensitivity of 83.3%, specificity of 75%, and area under the curve (AUC) of 0.935, indicating good diagnostic predictive value. Furthermore, despite the administration of SIB to positive pelvic lymph nodes, there was no significant increase in acute radiation toxicity. This difference might be closely related to the use of image-guided radiation therapy (IGRT) during the treatment process. IGRT takes into account the intrafraction and interfraction motion of the boost lymph nodes and dynamically adjusts the treatment conditions based on the organ and target position and shape changes. This ensures the accuracy of the radiation field, improves the control rate of metastatic lymph nodes, and reduces toxic reactions in surrounding normal organs [22].

Conclusion

In locally advanced cervical cancer patients with 2018 FIGO stage IIIC1r disease who underwent EFRT combined with VMAT and concurrent cisplatin chemotherapy, the observed toxicities were within clinically acceptable limits, with no grade 3 or higher acute/late toxicities. VMAT combined with EFRT and concurrent chemotherapy for locally advanced cervical cancer accompanied by bilateral pelvic lymph node metastasis and negative para-aortic lymph nodes may reduce the risk of para-aortic lymph node recurrence in the short term and potentially decrease the risk of distant para-aortic lymph node recurrence and distant metastasis, thereby prolonging disease-free survival and overall survival. The limitations of this study include the following: (1) The study primarily focused on observing the toxicity of EFRT, with a median follow-up period of only 27 months, which was insufficient for assessing late toxicity. Future studies should extend the follow-up period. (2) This retrospective study had a small sample size, resulting in persuasive conclusions that were relatively weak. (3) Larger, multicenter, prospective controlled studies are needed to further validate the safety and efficacy of EFRT in patients with locally advanced cervical cancer and high risk factors for PALM.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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