

Received: 2020.12.13

Accepted: 2021.05.18

Available online: 2021.06.11

Published: 2021.09.07

# Clinical Observation of Prophylactic Extended-Field Intensity-Modulated Radiation Therapy with Synchronous Chemotherapy in Locally Advanced Cervical Cancer

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Statistical Analysis C  
Data Interpretation D  
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**Financial support:** This study was supported by the Science and Technology Program of the Changzhou Health Commission (ZD202030, QN202047) and the Huzhou Scientific Program (2019GY57)

**Background:** We aimed to evaluate the value of prophylactic extended-field intensity-modulated radiation therapy (IMRT) in the treatment of locally advanced cervical cancer with multiple pelvic lymph node metastases ( $\geq 2$ ) and negative common iliac and paraaortic lymph nodes.

**Material/Methods:** Thirty-four patient with newly diagnosed cervical cancer (IB1-IVA) and multiple pelvic lymph node metastases ( $\geq 2$ ) confirmed by computed tomography and magnetic resonance imaging were randomly divided into an extended-field group (17 patients) and a pelvic-field group (17 patients). In the extended-field group, we added the drainage area of paraaortic lymph nodes on the pelvic field. The pelvic field was administered Dt 45.0 to 50.4 Gy, while the drainage area of paraaortic lymph nodes was administered Dt 40.0 to 45.0 Gy. Both groups were given Ir<sup>192</sup> intracavitary radiotherapy after 3 weeks of external irradiation. The total dose of point A was 25.0 to 30.0 Gy, fractional 6.0 to 7.0 Gy. All patients had concurrent platinum-based chemotherapy once weekly until the end of radiotherapy.

**Results:** No paraaortic lymph node metastasis was found in the extended-field group ( $P=0.0184$ ), and disease-free survival (DFS) was prolonged ( $P=0.0286$ ). Adverse effects in patients with III-IV degree myelosuppression were increased in the extended-field group ( $P=0.0324$ ). However, all patients recovered after symptomatic treatment.

**Conclusions:** Prophylactic extended-field IMRT with chemotherapy reduced the metastasis rate of paraaortic lymph nodes and prolonged the DFS in patients with locally advanced cervical cancer and multiple pelvic lymph node metastases ( $\geq 2$ ), while the toxic adverse effects were tolerated.

**Keywords:** Chemoradiotherapy • Radiotherapy, Intensity-Modulated • Uterine Cervical Neoplasms

**Full-text PDF:** <https://www.medscimonit.com/abstract/index/idArt/930457>

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## Background

Cervical cancer is a common malignant tumor in women. It ranks as the fourth most common malignant tumor in women in morbidity and mortality [1]. To date, radiotherapy, surgery, and chemotherapy are the major treatments for cervical cancer. For early-stage cervical cancer (IA-IIA), simple radical surgery or radical radiotherapy can be used with a good prognosis and a 5-year survival rate of more than 80% [2,3]. For middle-stage and locally advanced cervical cancer (IIB-IVA), concurrent chemo-radiotherapy is the main treatment, and the recurrence or uncontrolled rate fluctuates between 29% and 38% [4].

Para-aortic lymph node metastasis is a common treatment failure in advanced cervical cancer after chemo-radiotherapy [5,6], and the prognosis of patients with cervical cancer is significantly worse once para-aortic lymph node metastasis occurs after chemo-radiotherapy [7]. At present, extended-field (pelvic+para-aortic) radiotherapy is required for patients with locally advanced cervical cancer and positive common iliac or para-aortic lymph nodes, while for those with negative common iliac or para-aortic lymph nodes, the standard treatment is still platinum-based chemotherapy, concurrent with pelvic radiotherapy [8,9]. However, for patients with high-risk factors for para-aortic lymph node metastasis, there is still no consistent conclusion on whether to perform prophylactic extended-field radiotherapy [10,11].

The aim of our study was to evaluate the efficacy and toxicity of prophylactic extended-field intensity-modulated radiation therapy (IMRT) with synchronous chemotherapy in the treatment of locally advanced cervical cancer with multiple pelvic lymph node metastases ( $\geq 2$ ) and negative common iliac or para-aortic lymph nodes.

## Material and Methods

### Inclusion Criteria

The inclusion criteria were as follows: (1) age  $\leq 75$  years old; (2) Karnofsky performance score (KPS)  $\geq 70$ ; (3) no serious physical disease; (4) no distant metastases, including lung, liver, and bone; (5) IB1-IVA cervical cancer with multiple pelvic lymph node metastasis ( $\geq 2$ ) diagnosed by gynecological examination and pathology and confirmed by computed tomography (CT)/magnetic resonance imaging (MRI); and (6) patient had not undergone any other treatment. CT/MRI short diameter  $\geq 1$  cm or short diameter less than 1 cm but with a central low-density necrotic area was considered as the diagnostic criteria of pelvic lymph node metastasis in the present study [12]. The clinical staging was based on the 2009 Federation of Obstetrics and Gynecology (FIGO) clinical staging criteria [13].

### Clinical Information

We collected 34 cases of newly diagnosed cervical cancer (IB1-IVA) with multiple pelvic lymph node metastases ( $\geq 2$ ) confirmed by CT/MRI from December 2015 to November 2019 at the Changzhou Tumor Hospital. All selected patients voluntarily participated in the study and were randomly divided into 2 groups: an extended-field group (17 patients) and a pelvic-field group (17 patients). The patients were fully informed of the advantages and disadvantages of treatment and their respective adverse reactions. The groups were comparable in age, KPS, tumor size, pathological type, and clinical stage ( $P > 0.05$ ). The detailed clinical information of 34 patients is shown in **Table 1**. This research was approved by the Ethics Committee of the Changzhou Tumor Hospital Affiliated with Suzhou University.

### Treatment

All patients received IMRT combined with intracavitary brachytherapy. Patients were instructed to drink 800 mL water after fully emptying their bladder 40 min before CT positioning. The patients were fixed with a body membrane in the supine position. The CT scan area was obtained from the 10<sup>th</sup> thoracic vertebra to 10 cm below the ischial tubercle (slice thickness: 5 mm). The images were transmitted to the planning system (Eclipse, Varian, USA) for further radiotherapy planning design. In the extended-field group, we added the drainage area of the para-aortic lymph nodes on the pelvic field. The clinical target volume (CTV) included the para-aortic lymph nodes, intra iliac, extra iliac, presacral, obturator, and common iliac lymphatic drainage areas as well as the uterus, appendages, cervix, and vagina. The upper bound was the left renal vein, and the lower bound was determined by the invasion of the vagina. The CTV of the drainage area of the para-aortic lymph nodes was as follows: The anterior bound was 5 mm in front of the inferior vena cava and abdominal aorta, the posterior bound was the vertebral anterior border, and the bilateral bound was in the medial of the psoas muscle. The CTV delineation of the pelvic region was based on the CTV delineation guidelines recommended for radical radiotherapy of cervical cancer [14]. The planned target volume (PTV) was 0.7 cm, extended on the basis of the CTV, and appropriate modifications were made to the anatomical barrier and adjacent organs at risk. At the same time, we contoured the rectum, bladder, spinal cord, small intestine, and kidney as risk organs. The treatment plan was evaluated and optimized according to the dose (such as cold spot, hot spot), conformal degree, and dose volume histogram.

A Varian Clinac IX linear accelerator (6MV X-ray, IMRT) was used in this study, with a PTV prescription dose of 1.8 to 2.0 Gy per fraction, 5 times per week, and 25 to 28 fractions. The total dose was Dt 40 to 45 Gy in the para-aortic lymphatic drainage area and 45.0 to 50.40 Gy in the pelvic cavity. Dose requirements were 95% of PTV volume accepted as  $\geq$ prescription dose; 93%

**Table 1.** The 2 groups were comparable in age, Karnofsky performance score (KPS), tumor size, pathological type, and clinical stage ( $P>0.05$ ).

Group	Extended-field group (n=17)	Pelvic-field group (n=17)	$\chi^2$ value	P value
Median age	55	57		
Median KPS score	80	80		
Tumor size			0.23 (Fisher)	0.6282
<4cm	2 (11.76%)	3 (17.65%)		1
$\geq$ 4cm	15 (88.24%)	14 (82.35%)		
Pathological result			0 (Fisher)	1
Non-squamous cell carcinoma	1 (5.88%)	1 (5.88%)		1
Squamous cell carcinoma	16 (94.12%)	16 (94.12%)		
Clinical stage			3.31 (Fisher)	0.6518
IB	1 (5.88%)	0 (0.00%)		0.8845
IIA	1 (5.88%)	1 (5.88%)		
IIB	8 (47.06%)	10 (58.82%)		
IIIA	0 (0.00%)	1 (5.88%)		
IIIB	6 (35.29%)	5 (29.41%)		
IVA	1 (5.88%)	0 (0.00%)		

of prescription dose was  $\leq 1\%$ , and 110% of prescription dose was  $\leq 1\%$ . The dose limit of organs at risk were as follows: The irradiated volume of the rectum received more than 50.0 Gy exposure volume (V50)  $\leq 30\%$ ; bladder 50.0 Gy exposure volume (V50)  $\leq 30\%$ ; small intestine 30.0 Gy exposure volume (V30)  $\leq 40\%$ ; spinal cord maximum dose  $\leq 45.0$  Gy; and kidney 15.0 Gy exposure volume (V15)  $\leq 50\%$ . The superaddition dosage of parauterine or pelvic lymph nodes was made according to the gynecological and imaging examinations. The prescription dose was 6.0 to 8.0 Gy, 2.0 Gy/fraction, 3 to 4 times in total. After 3 weeks of external irradiation, Ir<sup>192</sup> intracavitary radiotherapy was given. The dosage of a point A prescription was 25.0 to 30.0 Gy, 6.0 to 7.0 Gy/fraction, and a total of 4 to 5 fractions.

Platinum-based synchronous chemotherapy was performed once per week until the end of radiotherapy. Patient vital signs and adverse reactions were closely observed during the period of treatment, and chemotherapy was stopped if necessary.

## Efficacy Evaluation

### Short-Term Efficacy Evaluation

Gynecological examination and pelvic CT/MRI were performed 1 to 3 months after the end of chemo-radiotherapy. The

short-term efficacy was evaluated by RECIST 1.1 as complete remission (CR), partial remission (PR), stable lesion (SD), or progression of disease (PD) [15].

### Evaluation of Recurrence and Metastasis

The patients were reexamined every 3 months in years 1 and 2, every 6 months in years 2 to 5, and yearly 5 years after the end of chemo-radiotherapy. The reexamination included gynecological examination, cervical/vaginal cytology, squamous cell carcinoma antigen (SCC Ag), thoracic CT, whole-abdomen CT/MRI, and bone emission-computed tomography. Local recurrence was defined as in-field recurrence, and distant metastasis was defined as out-field metastasis.

### Long-Term Efficacy Evaluation

Disease-free survival (DFS) and overall survival (OS) were observed. DFS was defined as the time from the beginning of treatment to no recurrence and metastasis in the last follow-up. OS was defined as the time from the beginning of treatment to death for any reason or the survival time at the last follow-up.

**Table 2.** There were no patients with paraaortic lymph node metastasis in the extended-field group and 6 patients with paraaortic lymph node metastasis (35.29%) in the pelvic-field group. The difference was statistically significant ( $P=0.0184$ ). There were no significant differences between the 2 groups in the pelvic recurrence rate and distant metastasis.

Groups	Pelvic recurrence	Paraaortic lymph node metastasis	Distant metastasis
Extended-field group (n=17)	3 (17.65%)	0 (0.00%)	2 (11.76%)
Pelvic-field group (n=17)	2 (11.76%)	6 (35.29%)	2 (11.76%)
<i>P</i> value (Fisher)	1	0.0184	1

### Evaluation of Adverse Reactions

Acute hematologic and nonhematologic toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 [16]. Late radiotherapy response was evaluated by the advanced radiation injury classification standard of the United States Cancer Radiotherapy Collaboration Group (RTOG) [17].

### Follow-Up

The follow-up time was from the beginning of treatment to death or the time of the last follow-up. The median follow-up period was 27 months (4-51 months), and the follow-up rate was 100%.

### Statistical Methods

This study was a prospective randomized controlled clinical trial. Thirty-four cases of newly diagnosed cervical cancer (IB1-IVA) with multiple pelvic lymph node metastases ( $\geq 2$ ) confirmed by CT/MRI were collected from December 2015 to November 2019 at the Changzhou Tumor Hospital. The primary endpoint was DFS. The secondary endpoints included 3-year OS and toxicity. Stata 14.0 statistical software was utilized for the statistical analyses. The short-term efficacy, metastasis, recurrence rate, and adverse reactions were analyzed by Fisher's exact probability test. Data were presented as the percentage of total samples that were assigned in each group. DFS and OS curves were done using the Kaplan-Meier test, and significance was determined by the log-rank test.  $P < 0.05$  was considered statistically significant.

## Results

### Short-Term Effects

The short-term efficacy evaluation of all of the 34 patients was evaluated as effective (response rate: CR+PR), without SD and PD. There were 14 patients with CR (82.35%) and 3 patients (17.65%) with PR in the extended-field group. There were 13 patients (76.47%) evaluated as CR and 4 patients (23.53%) as

PR in the pelvic-field group. There was no significant difference in the short-term efficacy between the 2 groups ( $P=1.0000$ ).

### Recurrence and Metastasis

Among the 34 patients, 3 (17.65%) had pelvic recurrence in the extended-field group, and 2 (11.76%) had pelvic recurrence in the pelvic-field group. There were 2 patients (11.76%) with distant metastases in both the extended-field group and pelvic-field group, and there was no significant difference between the 2 groups. In the extended-field group, no patients had paraaortic lymph node metastasis, but 6 patients (35.29%) had paraaortic lymph node metastases in the pelvic-field group, and the difference was statistically significant (Fisher's test,  $P=0.0184$ ) (Table 2).

### Long-Term Efficacy Evaluation

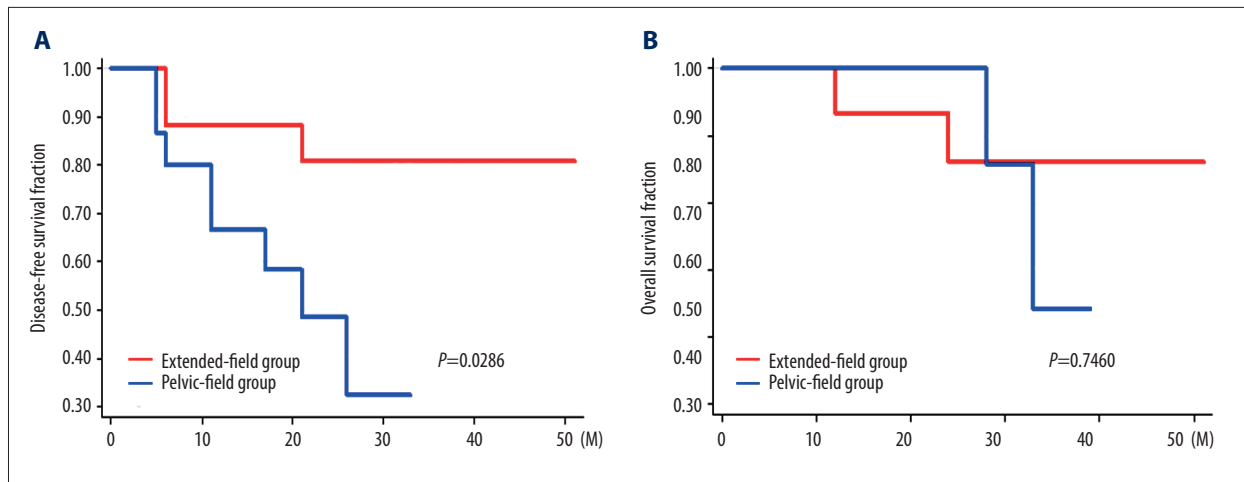
The DFS and OS rates of the 2 groups are shown in Figure 1. There was a significant difference in DFS between the 2 groups ( $\chi^2=4.79$ ,  $P=0.0286$ ). However, the 3-year survival rate was 86.15% in the extended-field group and 64.29% in the pelvic-field group. There was no significant difference in the 3-year OS rate between the 2 groups ( $\chi^2=0.10$ ,  $P=0.7460$ ).

### Adverse Reactions

There were 10 patients (58.82%) with III-IV degree myelosuppression in the extended-field group and 3 patients (17.65%) in the pelvic-field group, and the difference was statistically significant ( $P=0.0324$ ). However, there were no significant differences between the 2 groups in the occurrence of radiation enteritis and radiation cystitis (Table 3).

## Discussion

Synchronous chemo-radiotherapy is the primary treatment of middle-stage and locally advanced cervical cancer. Paraortic lymph node metastasis is a common cause of failure in advanced cervical cancer after chemo-radiotherapy. Moreover,



**Figure 1. (A, B)** The disease-free survival (DFS) was longer in the extended-field group than in the pelvic-field group ( $\chi^2=4.79$ ,  $P=0.0286$ ). The 3-year survival rate was 86.15% in the extended-field group and 64.29% in the pelvic-field group. There was no significant difference in 3-year overall survival between the 2 groups ( $\chi^2=0.10$ ,  $P=0.7460$ ).

**Table 3.** There were 10 patients (58.82%) with III-IV degree myelosuppression in the extended-field group and 3 patients (17.65%) with III-IV degree myelosuppression in the pelvic-field group; the difference was statistically significant ( $P=0.0324$ ). There were no significant differences between the 2 groups in the occurrence of radiation enteritis and radiation cystitis.

Group	Myelosuppression		Radiation enteritis		Radiation cystitis	
	I+II	III+IV	I+II	III+IV	I+II	III+IV
Extended-field group (n=17)	7 (41.18%)	10 (58.82%)	15 (88.24%)	2 (11.76%)	17 (100.00%)	0 (0.00%)
Pelvic-field group (n=17)	14 (82.35%)	3 (17.65%)	17 (100.00%)	0 (0.00%)	17 (100.00%)	0 (0.00%)
P value (Fisher)	0.0324		0.4848		1	

the prognosis of patients with cervical cancer is significantly worse once periaortic lymph node metastasis occurs after chemo-radiotherapy. Currently, pelvic radiotherapy with synchronous chemotherapy is still the standard treatment for patients with locally advanced cervical cancer and negative common iliac and paraaortic lymph nodes. However, for patients with high-risk factors of paraaortic lymph node metastasis, whether to undergo prophylactic extended-field radiotherapy is still under debate. A previous study declared that pelvic lymph node metastasis is an independent risk factor for paraaortic lymph node metastasis [18]. Multivariate analysis showed that FIGO stage III-IVA, SCC Ag >40 µg/L, advanced parauterine invasion, and positive pelvic lymph nodes are independent risk factors for recurrence and metastasis of paraaortic lymph nodes after pelvic radiotherapy. This study focused on patients with multiple pelvic lymph node metastasis ( $\geq 2$ ) and negative common iliac and paraaortic lymph nodes to evaluate the value of prophylactic paraaortic extended-field radiotherapy for locally advanced cervical cancer.

Several studies on extended-field radiation therapy with concurrent chemotherapy in locally advanced cervical cancer have

been conducted. A retrospective study was performed in patients with locally advanced cervical cancer and negative paraaortic lymph nodes in which a total of 62 patients received extended-field radiotherapy with synchronous chemotherapy, 71 patients received pelvic-field radiotherapy and synchronous chemotherapy, 26 patients received extended-field radiotherapy, and 44 patients received pelvic-field radiotherapy. The results showed that prophylactic paraaortic radiotherapy did not improve OS in the synchronous chemo-radiotherapy group [19]. Lee et al reviewed 206 cases of FIGO IB2-IVA cervical cancer patients (negative paraaortic lymph nodes) who received extended-field or pelvic-field IMRT. Among them, 20 patients (18.2%) in the pelvic-field group and 12 patients (12.5%) in extended-field group did not receive synchronous chemotherapy, and the remaining patients did receive synchronous chemotherapy. The 5-year survival rates of recurrence-free survival and OS in the pelvic-field and extended-field groups were 97.9% vs 87.6% ( $P=0.03$ ) and 87.8% vs 74.5% ( $P=0.04$ ), respectively. The results showed that prophylactic paraaortic radiotherapy improved the outcome of locally advanced cervical cancer [20]. A study conducted by Wakatsuki M et al was a prospective single-arm multi-institutional trial in which 95



cases were locally advanced cervical cancer with pelvic lymph node metastasis and without paraaortic metastasis in East and Southeast Asian countries. The 2-year local control, progression-free survival, and OS rates for all patients were 96%, 78%, and 90%, respectively. Acute grade 3 leukopenia was observed in 20 patients (21%), and late grade 3 gastrointestinal toxicity was observed in 3%. The results showed that the delayed prophylactic paraaortic radiotherapy decreased the rate of distant metastases and improved PFS and OS rates, without increasing toxicity [21].

Our study showed that there was no significant difference in short-term efficacy, pelvic recurrence, and distant metastasis rate between the 2 groups. Results showed that there were no patients with paraaortic lymph node metastasis in the extended-field group and 6 patients with paraaortic lymph node metastasis in the pelvic-field group. The prophylactic extended-field IMRT with synchronous chemotherapy decreased the metastasis rate of paraaortic lymph nodes ( $P=0.0184$ ), and DFS was significantly prolonged in the extended-field group ( $P=0.0286$ ). However, there was no significant difference in OS between the 2 groups ( $P=0.7460$ ). The present results are inconsistent with previous studies. A retrospective study conducted by Park et al showed the difference was due to a higher proportion of younger patients, positive pelvic lymph nodes, and larger tumor volume in the extended-field group, and the upper bound of each group's target area varied [19]. A study conducted by Wakatsuki et al was a prospective single-arm multi-institutional trial in which only IIB and IIIB stages were selected. The population examined was from East and Southeast Asian countries, the traditional radiotherapy technique was used, and the study spanned a long period (2007-2016). In addition, the study allowed various treatment methods based on the treatment situation of each country, rather than strict protocols. The present study is more innovative than the aforementioned studies in the following ways. First, it was a prospective randomized controlled clinical trial. Second, the cases were in the IB-IVA stage, and the individuals studied were exclusively Han Chinese who were born in areas south of the Yangtze River in China. Third, it contains recent data, with cases collected from December 2015 to November 2019. Fourth, all patients were uniformly treated with prophylactic extended-field IMRT with synchronous chemotherapy. Another significant reason for the difference between the present study and others is the lower number of patients and shorter follow-up time.

Traditional extended-field radiotherapy is controlled front and back or 4-field radiotherapy, which always produces severe adverse effects, especially with synchronous chemotherapy. Small et al (RTOG0116) used the traditional radiotherapy technique

in extended-field radiotherapy combined with synchronous chemotherapy of cisplatin and showed that the incidence of a III-IV degree acute radiotherapy reaction was 81% and the incidence rate of delayed radiotherapy reaction of degree III-IV was 40% [22]. Compared with conventional radiotherapy, extended-field IMRT can further improve the conformal degree between a high-dose distribution area and target area, deliver a more uniform dose distribution in the target area, and effectively limit the average dose and high-dose volume of organs at risk [23]. A retrospective study analyzed 55 patients with cervical cancer who received extended-field IMRT synchronous chemotherapy and 52 patients who received pelvic IMRT synchronous chemotherapy [24]. The incidence of III and IV degree acute adverse reactions was 34.5% and 19.2%, respectively. In a preventive extended-field IMRT synchronous chemotherapy trial, Kim et al found that the incidence of III-IV degree acute thrombocytopenia in the extended-field group was significantly higher than that in the pelvic-field group [25]. There was no difference in the incidence of III-IV degree gastrointestinal adverse reactions between the 2 groups. Yap et al reported that the incidence of advanced urogenital and gastrointestinal toxicity was 11% in the extended-field group and 8% in the pelvic-field group [26]. To reduce the toxicity of the treatment in the present study, we conducted IMRT. The III-IV degree myelosuppression (58.82%) in the extended-field group was higher than that in the pelvic-field group (17.65%) ( $P=0.0324$ ). There was no significant difference between the extended-field and pelvic-field groups in the occurrence of radiation enteritis and radiation cystitis. We concluded that although the myelosuppression can be increased in extended-field IMRT, the adverse effects are tolerable.

## Conclusions

This study shows that prophylactic extended-field IMRT with synchronous chemotherapy can reduce the metastasis rate of paraaortic lymph nodes and prolong DFS in patients who have locally advanced cervical cancer with multiple pelvic lymph node metastases ( $\geq 2$ ) and negative common iliac or paraaortic lymph nodes. The adverse effects were tolerable. However, the sample size in the present study was rather small. To further define the role of prophylactic extended-field IMRT in cervical cancer with high-risk factors, a multicenter prospective study with a large sample size is required.

## Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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