Clinical Analysis of Prophylactic Para-Aortic Intensity-Modulated Radiation in Cervical Cancer

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Research

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Abstract

Objective: To compare and evaluate survival, prognosis, treatment failure, and toxicity between two treatment regimens in cervical cancer patients radiologically diagnosed with pelvic lymphadenopathy and without para-aortic lymphadenopathy.

Methods: Thirty-one patients with cervical cancer were prospectively selected for primarily treatment as the extended-field, intensity-modulated radiation group (EF-IMRT group), and 37 patients were chosen simultaneously as the pelvic intensity-modulated radiation group (P-IMRT group). Both groups were diagnosed with pelvic lymphadenopathy without para-aortic lymphadenopathy before treatment by radiology. Pelvic and para-aortic IMRT was employed in the EF-IMRT group, with an upper exposed level of the left renal vein, while pelvic IMRT was employed in P-IMRT group. Both groups were treated with high dose rate ^{192}Ir brachytherapy and platinum-based concurrent chemotherapy.

Results: In the short-term, there was no effective difference between the groups. Regarding long-term efficacy, the 3-year overall survival (OS), progression-free survival (PFS), and progression and metastasis-free survival (PAMFS) in the EF-IMRT group and P-IMRT group were 87.0% vs. 74.6%, 83.6% vs. 61.7% and 96.0% vs. 80.5%, respectively. Treatment regimens, tumor size, and radiation time were all independent prognostic factors of OS and PFS. Treatment regimens, tumor size, and total equivalent dose in 2 Gy/f (EQD2) of point A were independent prognostic factors of PAMFS.

Conclusions: The risk of mortality, tumor progression, and metastasis in the para-aortic lymph nodes were significantly lower when using EF-IMRT than when using P-IMRT. EF-IMRT did not increase the incidence of gastrointestinal toxicities and genitourinary toxicities, and the toxicities at the late stages were mild.

Introduction

Cervical cancer is a common malignancy in the female reproductive tract, with the highest incidence in low- and middle-income countries[1]. Lymph node metastasis is a major route of cervical cancer spread and a vital predictor of prognosis[2]. The prognosis of patients with para-aortic lymph node (PALN) metastasis is worse than that of patients with pelvic lymph node (PLN) metastasis[3]. One prospective study[4] showed that the PALN metastasis rates of stage II and stage III cervical cancer confirmed by surgical and biopsy pathology were 20% and 37%, respectively. Once PALN metastasis of cervical cancer occurs, the treatment failure rate can reach 70%[5]. Therefore, it is crucial to prevent PALN metastasis after cervical cancer treatment, especially in advanced cases.

Few studies have focused on prophylactic, extended-field, intensity-modulated radiation treatment (EF-IMRT) of cervical cancer, and no consistent conclusion has been reached regarding the efficacy and toxicity of this treatment. In the present study, we recruited 31 patients with cervical cancer and pelvic lymphadenopathy but without para-aortic lymphadenopathy as the EF-IMRT group, as well as 37 such

patients as the pelvic intensity-modulated radiation group (P-IMRT group). The clinical efficacy, prognosis, and related complications in the two groups were examined to guide clinical work.

Materials And Methods

1.1 Baseline data

To construct the prophylactic EF-IMRT group, we recruited 31 patients with cervical cancer who were undergoing first-time treatment using this method in the Department of Gynecological Oncology of the Fourth Hospital of Hebei Medical University between August 2012 and August 2016. During the same period, we recruited 37 patients undergoing P-IMRT. None of the enrolled patients had undergone surgery, radiation, or chemotherapy related to their cervical cancer, and all had been diagnosed histopathologically with cervical squamous cell carcinoma before treatment. The following parameters were examined in all patients before treatment: blood routine, coagulation function, liver and kidney function, urine routine, squamous cell carcinoma antigen (SCC), carcinoembryonic antigen hematology, chest X-ray(orthotopic film), and whole abdominal computed tomography (CT) or magnetic resonance imaging (MRI) scan. In all patients, blood routine showed normal indexes, as did the liver and kidney function tests. Imaging revealed PLN metastasis in all patients, while those with PALN metastasis or metastasis at other sites were excluded. All patients had an Eastern Cooperative Oncology Group (ECOG) score of < 2 points. In the present study, lymph node metastasis was diagnosed when CT or MRI showed that the short diameter of the lymph nodes was > 1 cm, or that the short diameter of the lymph nodes was < 1 cm, but combined with central necrosis, ring enhancement, or capsular invasion. All patients were informed and consented to medical treatment by signing the relevant notices. This research has been performed in accordance with the principles stated in the Declaration of Helsinki. The study was approved by the Ethics Committee of The Fourth Hospital of Hebei Medical University.

1.2 Formulation and implementation of radiation plan

We devised guidelines with reference to the Radiation Therapy Oncology Group (RTOG) in the United States[6]. The following measurements were performed: gross tumor volume (GTV), defined as the volume of both the cervical mass and the pelvic lymph node metastasis and diagnosed by physical examination and clinical imaging; clinical target volume (CTV), which included the GTV combined with the volumes of the cervix, part of the vagina, uterus, parauterine, and drainage area of the pelvic lymph nodes (parauterine, obturator, internal and external iliac, presacral, and common iliac lymph nodes). The inguinal lymph node drainage area was included for patients with stage III A cancer, while the para-aortic lymph node drainage area was delineated in the EF-IMRT group. The planning target volume (PTV) was defined as the expansion of CTV in the L/R, A/P, and S/I directions by 0.7, 0.5, and 1 cm, respectively. The upper boundary of the CTV was the level of the left renal vein in the EF-IMRT group and between the upper and lower margins of waist 4 in the P-IMRT group, whereas the lower boundary in the two groups was set according to the scope of vaginal invasion. Enlarged pelvic lymph nodes were evenly dilated by 0.3cm to their planning GTV. With the PTV as the reference volume, the two groups were given a

prescribed dose of 45–50.4 Gy, 1.8–2 Gy/time, once per day, 5 times/week, with more than 95% of the PTV required to reach the prescribed dose. In the EF-IMRT group, the same prescribed dose was given in the abdominal para-aortic lymph node drainage area as in the pelvic area. With the planning GTV of the lymph nodes as the reference volume, the enlarged lymph nodes in the two groups were simultaneously pushed to 52–64.4 Gy. Intraluminalbrachy therapy was performed, with a dosage at point A of 6–7 Gy/time, 4–5 times, once per week, with a total dose of 24–33 Gy. With regards to chemotherapy, the patients were treated using 800–1000 mg/day tegafur for 5 consecutive days, as well as130 mg/m^2 oxaliplatin. Beginning on the first day, the patients were treated with chemotherapy at an interval of 3–4 weeks for 2–3 courses.

1.3 Evaluation criteria for efficacy and toxicity

The short-term efficacy was evaluated within 6 months of radiation therapy based on imaging examination, gynecological examination, and tumor markers. The efficacy evaluation criteria for solid tumors[7] were divided into complete response, partial response, stable disease, and progressive disease. Six months after radiation, the long-term efficacy was evaluated according to the patient's symptoms, imaging, gynecological examination, and tumor markers. Any local pelvic tumor was defined as recurrence, and any tumor beyond the pelvic cavity was defined as metastasis. Para-aortic lymph node metastasis was not defined as distant metastasis.

Acute toxicities were defined as treatment-related toxic reactions that occurred 3 months from the start to the end of radiation, evaluated according to the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAEv4.0)[8]. Long-term toxicity was defined as treatment-related toxic reactions within 3 months of the end of radiation, evaluated according to the RTOG classification criteria.

1.4 Statistical analysis

Statistical analysis was performed using SPSS 21.0 (IBM, Armonk, NY, USA) statistical software. The *t*-test or rank-sum test was used to compare baseline data and measurement data between the two groups. The chi-square test was used to compare count data, failure modes, and acute and late toxicity between the two groups. The Kaplan–Meier method was adopted to calculate overall survival (OS), progression-free survival (PFS), and progression- and metastasis-free survival (PAMFS). Survival curves were plotted on this basis. The log-rank test was used for univariate survival analysis. The time-dependent covariate method was used to test the Cox proportional hazards hypothesis. The Cox proportional hazards regression model was used for multivariate survival analysis. The significance level was $\alpha = 0.05$, and P-values < 0.05 were determined as statistically significant.

Results

Therapeutic efficacy

With regards to short-term efficacy, 6 months after radiation, the EF-IMRT group reached a complete response rate of 100%. In the P-IMRT group, one case of cervical cancer and two cases of para-iliac lymph node metastasis were uncontrolled, but showed partial response; the remaining patients reached complete response, resulting in a complete response rate of 91.89%. There was no statistical difference between the two groups in this regard (P = 0.304). In terms of long-term efficacy, at the final follow-up, there were five cases of recurrence or metastasis in the EF-IMRT group and 14 cases in the P-IMRT group. PALN metastasis occurred in one case in the EF-IMRT group and seven cases in the P-IMRT group. Among these seven cases, three had solitary metastasis, three had distant metastasis, and one had local PLN recurrence. In the EF-IMRT and P-IMRT groups, there were one and five cases of local recurrence, respectively, as well as five and 13 cases of metastasis (including PALN). As a result, the local recurrence and metastasis rates (including PALN metastasis) in the EF-IMRT group were 3.23% and 13.51% (P = 0.289), respectively, while those in the P-IMRT group were 12.90% and 35.14% (P = 0.035).

Prognostic factor analyses

The univariate survival analysis included treatment regimen, age, FIGO stage, tumor size, pre-treatment SCC level, pre-treatment hemoglobin level, total radiation time, total equivalent dose in 2 Gy/f(EQD2) at point A, and number of metastatic PLNs. A log-rank test was performed on these variables. The results showed that tumor size (P = 0.000) and total radiation time (P = 0.001) were related to the prognosis of OS. The following factors were significantly related to the prognosis of PFS: treatment regimen (P = 0.037), tumor size (P = 0.000), total radiation time (P = 0.037), and FIGO stage (P = 0.047). The following factors were related to the prognosis of PAMFS at point A: treatment regimen (P = 0.048), tumor size (P = 0.028), and total EQD2 (P = 0.025). The univariate analysis is shown in Table 1. The number of cases not treated with chemotherapy in the two groups was too small and not included in the univariate analysis.

Table 1
Univariate analysis of survival rates

Prognostic factors	3-year OS		3-year PFS		3-year PAMFS	
	%	P-value	%	P-value	%	P-value
Treatment regimens		0.161		0.037		0.048
EF-IMRT	87.0		83.6		96.0	
P-IMRT	74.6		61.7		80.5	
Age		0.710		0.965		0.587
< 50 year	78.5		75.0		89.2	
≥ 50 year	80.6		70.0		87.2	
FIGO stage		0.373		0.047		0.390
	100.0		100.0		100.0	
	84.6		79.7		91.1	
	69.6		53.8		78.6	
Tumor size		0.000		0.000		0.028
≤ 5 cm	93.5		88.5		94.0	
> 5 cm	65.2		53.0		78.6	
SCC-Ag level		0.090		0.113		0.326
< 10 ng/mL	87.8		77.8		88.9	
≥ 10 ng/mL	72.2		65.7		87.0	
HB		0.134		0.077		0.270
< 110 g/L	70.6		54.3		77.5	
≥ 110 g/L	83.1		73.7		90.9	
Radiation time		0.001		0.037		0.663
≤ 56 days	100.0		84.1		90.1	
> 56 days	61.4		60.8		86.0	
EQD2 for point A		0.424		0.783		0.025

OS, overall survival; PFS, progression-free survival; PAMFS, para-aortic lymph node metastasis-free survival

Prognostic factors	3-year OS		3-year PFS		3-year PAMFS	
	%	P-value	%	P-value	%	P-value
< 85 Gy	87.8		64.7		68.8	
≥ 85 Gy	77.7		74.4		95.5	
Number of pelvic lymphadenopathies		0.136		0.431		0.224
≤ 2	85.9		75.5		91.9	
> 2	75.3		68.1		83.8	
OS, overall survival; PFS, progression-free survival; PAMFS, para-aortic lymph node metastasis-free survival						

The Cox proportional hazards hypothesis was tested using the time-dependent covariate method for the following parameters: treatment regimen, age, FIGO stage, tumor size, pre-treatment SCC level, pre-treatment hemoglobin level, total radiation time, total EQD2 at point A, and number of metastatic PLNs. The results showed that FIGO stage did not satisfy the constant Cox proportional hazards of OS and PAMFS, whereas all other factors satisfied the constant proportional hazard of OS, PFS, and PAMFS (Table 2).

Table 2
The results of the proportional hazards assumption in the Cox regression

Characteristics	OS		PFS		PAMFS	
	χWald2	P-value	χWald2	P-value	χWald2	P-value
Treatment regimens	0.018	0.892	0.000	0.994	0.252	0.616
Age	1.728	0.189	2.869	0.090	1.075	0.300
FIGO stage	4.319	0.038	1.685	0.194	2.109	0.039
Tumor size	0.387	0.534	0.007	0.932	0.000	0.987
SCC-Ag level	0.295	0.587	0.737	0.391	0.573	0.449
HB	0.318	0.573	0.067	0.796	0.806	0.369
Radiation time	1.366	0.243	1.109	0.796	0.721	0.396
EQD2 for point A	0.078	0.780	2.195	0.138	0.036	0.850
Number of pelviclymph-adenopathies	1.413	0.235	0.672	0.412	0.036	0.849

After FIGO stage was excluded, the following factors were included in the multivariate survival analysis of OS and PAMFS: treatment regimen, age, tumor size, pre-treatment SCC level, pre-treatment hemoglobin level, total radiation time, total EQD2 at point A, and number of metastatic PLNs. The above factors, including FIGO stage, were included in the multivariate survival analysis PFS. The results showed that treatment regimen, tumor size, and total radiation time were independent prognostic factors of OS and PFS, and that treatment regimen, tumor size, and total EQD2 at point A were independent prognostic factors of PAMFS. The results of the multivariate analysis are shown in Table 3 and indicated significant interactions among various factors. After correction by Cox multivariate prognostic analysis, the treatment regimen, i.e.prophylactic extended-field radiation, was an independent prognostic factor of OS, PFS, and PAMFS. The risk of mortality, disease progression, and PALN metastasis in the P-IMRT group were 4.764, 6.097, and 11.318 times higher than those in the EF-IMRT group.

Table 3
Multivariate analysis of survival rates

Prognostic factors	**OS**		**PFS**		**PAMFS**	
	HR (95%CI)	**P-value**	**HR (95%CI)**	**P-value**	**HR (95%CI)**	**P-value**
Treatment regimens		**0.010**		**0.001**		**0.027**
EF-IMRT	1		1		1	
P-IMRT	4.764 (1.448–15.678)		6.097 (2.090–17.788)		11.318 (1.311–97.733)	
Tumor size		**0.002**		**0.000**		**0.003**
≤ 5 cm	1		1		1	
> 5 cm	11.642(2.529–53.581)		9.186 (2.853–29.575)		14.841(2.552–86.314)	
Radiation time		**0.011**		**0.034**		
≤ 56 days	1		1			
> 56 days	7.172(1.569–32.783)		2.972 (1.087–8.124)			
EQD2 for point A						**0.027**
< 85Gy					5.218 (1.206–22.571)	
≥ 85Gy					1	

Toxicity

No fatal toxicities (grade 5) occurred in any of the patients enrolled. Three cases in each group had acute,grade 3 gastrointestinal reactions (P = 1.000), butno acute, grade 3 or above genitourinary reactions occurred. With regards to acute hematological toxicity, there was significantly more leukopenia of grade 3 or above in the EF-IMRT group than in the P-IMRT group (P = 0.038), with 16 cases (51.61%) and 10 cases (27.03%), respectively, and there was a significant difference between the two groups (P = 0.047). There were 17 cases (54.84%) of thrombocytopenia in the EF-IMRT group and 11 cases (29.93%) in the P-IMRT group, constituting a significant difference between the two groups (P < 0.036). Among these cases, only onein each group showed reactions of grade 3 or above (P = 1.000). Elevenpatients (35.48%) in the EF-IMRT group and nine (24.32%) in the P-IMRT group sustained liver injury during radiation and chemotherapy, but there was no significant difference between the two groups. None of the patients had renal injury in either group. Treatment interruptions due to severe acute reactions of grade 3 or above occurred within 5 weeks of the start of the treatment. None of the patients enrolledshowed late toxicities of grade 3 or above, and the most severe late gastrointestinal reaction was hematochezia. Intermittent hematochezia occurred in five cases (16.1%) in the EF-IMRT group and three cases (8.1%) in the P-IMRT group. These incidents were relieved after conservative treatments such as enema and drugs. The toxicity measurements are shown in Table 4.

Table 4
Acute and late toxicity in the EF-IMRT and P-IMRT groups

Toxicities	EF-IMRT				P-IMRT				P-value
	G1	G2	G3	G4	G1	G2	G3	G4	
Acute Toxicities									
Gastrointestinal	7	4	3	0	15	4	3	0	0.239
Genitourinary	0	0	0	0	1	1	0	0	0.496
Hematological									
Leukopenia	4	6	10	6	2	11	9	1	0.047
Anemia	5	15	0	0	6	13	0	0	0.274
Thrombo-cytopenia	8	8	0	1	7	3	0	1	0.036
Hepatic function	7	4	0	0	6	1	2	0	0.314
Late Toxicities									
Gastrointestinal	2	5	0	0	5	4	0	0	0.866
Genitourinary	3	0	0	0	2	0	0	0	0.837

Discussion

Lymph node metastasis is the main mode of cervical cancer metastasis, and the most common mode of lymph node metastasis in cervical cancer is progressive metastasis from the pelvic lymph nodes to the common iliac and para-aortic lymph nodes, and finally to distant metastasis. PALN metastasis is closely related to the status and number of PLN metastases [9]. In patients with PLN metastasis, the risk of PALN metastasis is significantly increased [10, 11]. The scope of routine radical surgery and radiation to treat cervical cancer does not contain the drainage area of the PALN, but patients with positive PLN metastasis may have micrometastas is in the PALN[12], which can result in PALN and distant metastases that form after treatment. Positron emission tomography (PET)/CT is used to evaluate the lymph nodes. This method has high diagnostic sensitivity, but cannot completely exclude lymph node metastases with small diameter[13]. Therefore, patients with cervical cancer and PLN metastasis may benefit from prophylactic radiation of the PALN to reduce recurrence and metastasis.

At the end of the 20th century, five large-scale clinical studies investigated cisplatin-based concurrent radiation and chemotherapy [14–18]. They confirmed that radiation combined with chemotherapy was important in the treatment of cervical cancer. Park et al. [19]retrospectively reviewed the efficacy of extended-field concurrent radiation and chemotherapy to treat locally advanced cervical cancer. Out of 88 cases in the para-aortic group and 115 in the pelvic group, 62 cases and 71 cases received chemotherapy, respectively. In the patients treated with concurrent chemotherapy, the 5-year survival rates in the para-aortic and pelvic groups were 72.3% and 84.3%, respectively (P = 0.140). In patients who were not treated with chemotherapy, the 5-year survival rates in the para-aortic and pelvic groups were 72.1% and 60.5%, respectively (P = 0.056), and PALN metastasis occurred in four cases in the para-aortic group and three cases in the pelvic group. The researchers concluded that prophylactic radiation of the PALN, especially when combined with chemotherapy, could not improve the prognosis of patients with advanced cervical cancer. However, in that study, the rate of PALN metastasis was high, the diameter of the local tumor was large, and traditional four-field box radiation was applied. All these factors may have affected the efficacy of extended-field radiation. Since the start of the 21st century, high-precision radiation technology has developed rapidly. Intensity-modulated radiation has been widely applied in radiation centers, which can minimize the tolerable dose in normal tissues[20]. Thus, some researchers have investigated the efficacy of extended-field intensity-modulated radiation combined with chemotherapy. Asiri et al.[21] applied concurrent chemotherapy and radical radiation to treat locally advanced cervical cancer. Thirty-six cases and 38 cases were randomized into the pelvic and para-aortic groups, respectively. Both groups were treated with 40 mg/m^{2}of cisplatin therapy weekly. External radiation was performed using 3-dimensional conformal radiation and IMRT techniques, whereas internal radiation was performed using high dose rate ^{192}Ir brachytherapy. The 5-year survival rates in the para-aortic and pelvic groups were 72.4% and 60.4%, respectively (P = 0.04), and the PFS rates were 80.3% and 69.1%, respectively (P = 0.03), with one case (2.6%) and five cases (13.9%) of PALN metastasis, respectively. The above studies arrived at no unified conclusion regarding the efficacy of extended-field radiation combined with chemotherapy. As no detailed evaluation of the pelvic lymph node status was carried out, the baseline data of the experimental and control groups were unbalanced, leading to large differences in results across studies. In the present

study, no significant differences occurred in the number of metastatic PLNs between the para-aortic and pelvic groups. We employed IMRT external radiation and high dose rate ^{192}Ir brachytherapy, and all patients completed radiation, with only one patient in each group receiving no chemotherapy. The 3-year survival rates in the present study were higher than in the study by Asiri et al.—87.0% in the para-aortic group and 74.6% in the pelvic group. Univariate analysis indicated no difference in OS rate between the two groups, but Cox multivariate analysis revealed a significant difference after correction. This discrepancy may have occurred because of the small sample size, short follow-up time, and interactions among influencing factors. In the PFS and PAMFS survival analysis, the 5-year PFS (P = 0.000) and PAMFS (P = 0.027) in the EF-IMRT group were appreciably longer than those in the P-IMRT group, and the difference was significant in both cases. These results were similar to those of recent studies. Liang et al. [22]recruited patients with cervical cancer and PLN metastasis but without PALN metastasis; this approach somewhat reduced the error caused by PLN, and the 3-year OS rates were the same as in the present study. Lee et al. [23]suggested that OS and PFS were significantly higher in the para-aortic group than in the pelvic group in patients with PLN metastasis, but there was no significant difference between the two treatment groups in patients without PLN metastasis. There were three cases (3.1%) and 13 cases (11.8%) of PALN metastasis in the para-aortic and pelvic groups, respectively (P = 0.02), and the 5-year PAMFS was 97.9%. In the present study, one case (3.23%) in the para-aortic group and seven cases (18.92%) in the pelvic group had PALN metastasis (P = 0.105), and the 3-year PAMFS was 96.0%. Both studies showed satisfactory control over PALN. In addition, the distant metastasis rate in the EF-IMRT group was below 10% in the present study, and the extrapelvic metastasis rate was significantly lower than that in the P-IMRT group (P = 0.035). The above analysis suggests that extended-field radiation combined with chemotherapy to treat high-risk patients with cervical cancer and PLN metastasis may improve survival prognosis and reduce the treatment failure rate to varying degrees. However, this conclusion requires further study with a larger number of cases.

In recent years, many researchers have attempted to identify risk factors for the recurrence and metastasis of cervical cancer, and several have given prophylactic treatments to high-risk patients to prolong survival time. After examining the pathological factors related to PALN metastasis, Chen et al. [30]suggested that clinical stage, histological grade, depth of cervical interstitial invasion, tumor size, para-uterine invasion, vascular tumor thrombus, and PLN metastasis were all associated with PALN metastasis, whereas pre-treatment SCC level, age, and pathological type were not. Some other researchers believe that treatment, FIGO stage, and pathological type are independent factors that affect prognosis [24]. This suggests that study endpoints and outcomes vary among centers. Thus, researchers must examine and identify relevant prognostic factors that are clinically available before treatment. Cervical cancer is classified as local, early-stage or locally advanced, with a 4-cm cut-off. However, the present study focused on locally advanced cervical cancer and investigated independent risk factors for OS, PFS, and PAMFS with tumor size > 5 cm (cut-off). The findings accorded with those of a study by Han et al.[25]. A Korean study[26] attempted to predict the risk of PALN metastasis and showed that tumor size on magnetic resonance imaging and PALN status on PET/CT were independent predictors of PALN metastasis. Based on these two factors, the investigators established a PALN recurrence prediction

model, which assigned 0, 1, and 3 points to patients with tumor size ≤ 4 cm, 4–5 cm, and > 5 cm, respectively. The model produced good predictions, and the investigators recommended concurrent chemotherapy with extended-field PALN + pelvic radiation in patients with high scores. The present study corroborated that model, showing that a tumor size > 5 cm can reduce PAMFS significantly. A previous study [26]indicated that radiation time could dramatically affect the prognosis of cervical cancer: for every 1 day extension of radiation time over 55 days, the survival rate and local control rate were reduced by 0.6% and 0.7%, respectively. Lin et al. [27] also found that, in patients with stage I–II B cervical cancer, the 5-year survival rate with a total radiation time of ≤ 56 days was significantly higher than that with a total radiation time of > 56 days (70% vs. 65%, respectively, P = 0.002). The present study revealed that the risk of mortality and disease progression with a total radiation time of > 56 days was 6.131 and 3.021 times higher than that with a total radiation time of ≤ 56 days. The American National Comprehensive Cancer Network guidelines recommend a radiation dose of EQD2 ≥ 85 Gy to treat locally advanced tumors, and emphasize that an adequate dose (45 Gy) should be given during extended-field radiation to patients with occult metastasis or micrometastas is in the PALN. The present study confirmed this view, with the risk of PALN metastasis at point A in the EQD2 ≥ 85 Gy group being significantly lower than that in the EQD2 < 85 Gy group (P = 0.027). The probability of PALN metastasis is significantly higher in patients with PLN metastasis than in those without. Nevertheless, few studies have measured the effect of the number of metastatic PLNs on PALN metastasis. Wei et al. [16]found that the probability of PALN metastasis increased with the number of metastatic PLNs. Zeng et al. [9]suggested that a positive PLN count of ≥ 2was more likely to cause PALN metastasis. In the present study, pelvic lymph nodes were grouped, with ≥ 2 as the cut-off count, but there were no differences in OS, PFS, and PAMFS between the group with ≥ 2 positive PLNs and that with < 2. In imaging, there were marked differences in shape and size of the metastatic PLNs, as well as number. There was one case of lymphadenopathy with a tumor size of > 2 cm, which may have affected the findings. It follows that the lymph node screening scheme should be further improved. In summary, with regards to tumor characteristics, a tumor size of > 5 cm results in poor survival prognosis. These findings will inform the screening of high risk patients at for recurrence, as well as the timely prevention and intervention of PALN in clinical work. In terms of treatment, prophylactic radiation of the PALN should be given to high-risk patients, with a total dose of EQD2 ≥ 85 Gy at point A, and the total radiation time should be kept within 8 weeks as much as possible to improve the efficacy and reduce the risk of recurrence and metastasis.

Regarding treatment-related toxicities, the present study demonstrated that only acute hematological toxicity reached grade 4. There was significantly more leukopenia in the EF-IMRT group than in the P-IMRT group, with 16 cases (51.61%) and 10 cases (27.03%) of leukopenia of grade 2 or above, respectively (P = 0.038). There was no significant difference in late reaction between the two groups, and no toxicity of grade 3 took place. All patients with leukopenia were corrected to the normal range after timely treatment with elevated leukocytes, and no patients developed agranulocytosis with fever and related death. Oh et al. [29]found that the acute gastrointestinal reaction in the para-aortic group was significantly higher than that in the pelvic group (40.4% vs. 35.1%, P = 0.046), with no significant difference in late reaction between the two groups. The authors stressed that stronger gastrointestinal

reactions did not affect the completion rate of radiation *in vitro*, and that overall toxicity was tolerable. Several studies have demonstrated that the acute toxicity of concurrent radiation and chemotherapy were mild, all late reactions were tolerable, and that toxicity was not significantly higher in the para-aortic group than in the pelvic group [19, 21]. Furthermore, Park et al. emphasized that late reactions of grade 4 in the para-aortic group, such as rectal perforation in the pelvis, might be unrelated to extended-fieldradiation. As such, extended-fieldradiation with concurrent chemotherapy may increase acute reactions, but the reactions was controllable and do not increase late toxicity.

The present study revealed that prophylactic intensity-modulated radiation combined with chemotherapy to treat PALN metastasis can improve survival prognosis in high-risk patients with cervical cancer, with more tolerable toxicities than conventional radical pelvic radiation and chemotherapy. However, because we only used a small sample size and a short follow-up time, the evaluation of lymph node status using contrast-enhanced CT or MRI scan may have contained errors. In future work, we need to expand the sample size, pay attention to the shape and size of lymph nodes, and improve the PLN evaluation.

Abbreviations

PALN
Para-aortic lymph node; PLN:pelvic lymph node; EF-IMRT:Extended-field, intensity-modulated radiation treatment; SCC:squamous cell carcinoma antigen; CT:Computed tomography; MRI:Magnetic resonance imaging; ECOG:Eastern Cooperative Oncology Group; RTOG:Radiation Therapy Oncology Group; GTV:Gross tumor volume; PVT:planning target volume; OS:Overall survival; PFS:Progression-free survival; PAMFS:Progression- and metastasis-free survival.

Declarations

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None.

Authors' contributions

All authors helped to perform the research; Ge Ji and Xiaomei Fan manuscript writing and performing data analysis; Ge Jin, Kuixiu Li, Shuhuai Niu, and Siyang Liu performing data analysis; Xiaomei Fan and Qianying Zhang drafting conception and design. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

We conducted a retrospective observational study and used the “opt-out” method as a way to obtain informed content from patients. The study was approved by the Ethic Committee of The Fourth Hospital of Hebei Medical University.

Consent for publication

We have obtained the consent for publication from all patients.

Competing interests

The authors declare that they have no competing interests

References

1. Ginsburg O, Bray F, Coleman MP, et al. The global burden of women’s cancers: a grand challenge in global health[J]. The Lancet. 2017;389(10071):847–60.
2. Hu Yan,Chang Xiaobin,Wang Guoqing, et al.Analysis of prognostic factors of cervical cancer in 538 cases. Shaanxi Medical Journal, 2017(11): 1531–1534.
3. Du JunyaoZhang. Xin,Li Liankun.Outcomes and prognostic factors of cervical cancer in 264 patients of stage â□□b-â□¢.Chinese Journal of Practical Gynecology and Obstetrics, 2015(02): 137–141.
4. Tsunoda AT, Marnitz S, Soares Nunes J, et al. Incidence of Histologically Proven Pelvic and Para-Aortic Lymph Node Metastases and Rate of Upstaging in Patients with Locally Advanced Cervical Cancer: Results of a Prospective Randomized Trial[J]. Oncology. 2017;92(4):213–20.
5. Manders D, Kehoe S, Richardson D, et al. Cervical cancer — Distant failure after treatment of para-aortic lymph node metastases[J]. Gynecol Oncol. 2014;135(2):389.
6. Lim K, Small W, Portelance L, et al. Consensus Guidelines for Delineation of Clinical Target Volume for Intensity-Modulated Pelvic Radiation for the Definitive Treatment of Cervix Cancer[J]. International Journal of Radiation Oncology*Biology*Physics. 2011;79(2):348–55.
7. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)[J]. Eur J Cancer. 2009;45(2):228–47.
8. Common Terminology Criteria Adverse Events. (CTCAE).Version 4.0.U.S. Department of health and human services.National Institutes of Health.National Cancer Institute 2009.
9. Wensheng ZWei,Xu, Xu H,et al. The Clinical Value of Para-aortic Lymphadenectomy in Patients with Cervical Cancer in Stage â□ B2 and â□□A2. Journal of Practical Obstetrics and Gynecllogy, 2013(03): 206–210.

10. Wei Y,Yao Desheng,Li Fei,et al.Analysis of risk factors of cervical carcinoma with para-aortic lymph node metastasis. Chinese Journal of Cancer Prevention and Treatment, 2013(14): 1110–1112.
11. Huang E-Y, Wang C-J, Chen H-C, et al. Multivariate Analysis of Para-Aortic Lymph Node Recurrence After Definitive Radiation for Stage IB-IVA Squamous Cell Carcinoma of Uterine Cervix[J]. International Journal of Radiation Oncology*Biology*Physics. 2008;72(3):834–42.
12. Martínez A, Mery E, Ferron G, et al. Incidence of micrometastases in histologically negative para-aortic lymph nodes in advanced cervical cancer patients[J]. Gynecol Oncol. 2010;119(1):76–80.
13. Atri M, Zhang Z, Dehdashti F, et al. Utility of PET-CT to evaluate retroperitoneal lymph node metastasis in advanced cervical cancer: Results of ACRIN6671/GOG0233 trial[J]. Gynecol Oncol. 2016;142(3):413–9.
14. Green JA, Kirwan JM, Tierney JF, et al. Survival and recurrence after concomitant chemotherapy and radiation for cancer of the uterine cervix: a systematic review and meta-analysis[J]. Lancet. 2001;358(9284):781–6.
15. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma[J]. N Engl J Med. 1999;340(15):1154–61.
16. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer[J]. N Engl J Med. 1999;340(15):1137–43.
17. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiation and chemotherapy for locally advanced cervical cancer[J]. N Engl J Med. 1999;340(15):1144–53.
18. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study[J]. J Clin Oncol. 1999;17(5):1339–48.
19. Park SG, Kim JH, Oh YK, et al. Is Prophylactic Radiation to Para-aortic Lymph Nodes in Locally Advanced Cervical Cancer Necessary?[J]. Cancer Research Treatment: Official Journal of Korean Cancer Association. 2014;46(4):374–82.
20. Gandhi AK, Sharma DN, Rath GK, et al. Early clinical outcomes and toxicity of intensity-modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized study[J]. Int J Radiat Oncol Biol Phys. 2013;87(3):542–8.
21. Asiri MA, Tunio MA, Mohamed R, et al. Is extended-field concurrent chemoradiation an option for radiologic negative paraaortic lymph node, locally advanced cervical cancer?[J]. Cancer Management Research. 2014;6:339–48.
22. Liang J-A, Chen S-W, Hung Y-C, et al. Low-dose, prophylactic, extended-field, intensity-modulated radiation plus concurrent weekly cisplatin for patients with stage IB2-IIIB cervical cancer, positive pelvic lymph nodes, and negative para-aortic lymph nodes[J]. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society. 2014;24(5):901–7.

23. Lee J, Lin J-B, Chang C-L, et al. Prophylactic lower para-aortic radiation using intensity-modulated radiation mitigates the risk of para-aortic recurrence in locally advanced cervical cancer: A 10-year institutional experience[J]. Gynecol Oncol. 2017;146(1):20–6.
24. Wang J,Xu Kekui,Shi Baigao,et al. An Analysis of Prognostic Factors in 4374 Cases with Cervical Cancer. China Cancer, 2014(04): 281–288.
25. Han Z,Tian Xiaofei,Han Xingmei,et al.Journal of Modern Oncology, 2015(05): 692–694.
26. Shim S-H, Kim D-Y, Lee SJ, et al. Prediction model for para-aortic lymph node metastasis in patients with locally advanced cervical cancer[J]. Gynecol Oncol. 2017;144(1):40–5.
27. Petereit DG, Sarkaria JN, Chappell R, et al. The adverse effect of treatment prolongation in cervical carcinoma[J]. International Journal of Radiation Oncology*Biology*Physics. 1995;32(5):1301–7.
28. Lin SM, Ku HY, Chang TC, et al. The prognostic impact of overall treatment time on disease outcome in uterine cervical cancer patients treated primarily with concomitant chemoradiation: a nationwide Taiwanese cohort study[J]. Oncotarget. 2017;8(49):85203–13.
29. Oh J, Seol KH, Lee HJ, et al. Prophylactic extended-field radiation with concurrent chemotherapy for pelvic lymph node-positive cervical cancer[J]. Radiat Oncol J. 2017;35(4):349–58.
30. Chen D,He Hongying,Tan Guangping.Influencing factors of para-aortic lymph node metastasis in early cervical cancer. Journal of Baotou Medical College, 2017(01): 1–2 + 5.